# Sleep as a behavioral and physiological correlate of intellectual ability in healthy children

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by
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# Abstract

Sleep and waking behavior are mutually dependent and in close interaction with each other. For example, cognitive performance may be impaired by a lack of sleep.

To specify the relationship between sleep and cognition, it is essential to differentiate between two fundamental concepts: traits and states. *Traits* represent behavioral or biological dispositions which are empirically or statistically established, fairly stable over time and independent from actual situations or tasks. In contrast, *states* are characterized by temporariness and situational fluctuations.

Intelligence which is characterized by a high long-term intra-individual stability and heritability is considered to be a trait. Cognitive processes, on the other hand, are state-dependent and thus relate to a specific performance, for example performance in a perceptual motor learning task or a verbal learning paradigm. The distinction between traits and state-dependence is, however, also important for sleep. Many studies allude to the influence of experimental sleep manipulations on the subsequent sleep pattern and the sleep EEG on the state-level. However, the human sleep pattern also qualifies for a trait, which has largely been disregarded so far in experimental research protocols. Behaviorally, it is known that sleep duration and chronotype represent characteristic individual features. It is also likely that certain aspects of sleep architecture and regulation are under genetic control. The sleep EEG has even been described as a trait-like "fingerprint", probably reflecting traits of the underlying brain anatomy. In children, this trait-like characteristic of the sleep EEG has, however, not yet been investigated.

Despite the general acceptance of trait definitions for both sleep and intelligence, surprisingly little research is documented about the potential relationship between the two phenomena. In children, even less is known about this association. Although there are a few studies on clinical populations and the effects of sleep restriction on children's cognitive outcome, there is up to now no comprehensive work on the trait-like association between sleep and intelligence in healthy children. Besides, many assumptions about children's sleep behavior

and its relation to daytime performance are shaped by intuition and beliefs rather than scientific evidence.

This doctorial thesis attempts to identify behavioral and physiological variables of children's sleep in its relationship with intellectual ability. In particular, the aim is to describe potential relationships on the trait-level. Sleep behavior and pattern was assessed by subjective and objective tools (questionnaires, actigraphy and sleep EEG), which characterizes sleep on qualitative as well as on quantitive dimensions. Using a multidimensional intelligence test (German version of the WISC-IV), full scale IQ scores as well as scores for various sub-indices (verbal and fluid IQ, working memory, speed of processing) were assessed, enabling for a comprehensive characterization of children's intellectual ability.

The following main results were obtained: First, children's sleep EEG can be considered a trait. Sleep stage distribution and spectral power was highly correlated between the two nights of the same child, with a large intra-individual similarity and inter-individual variability. Second, there are associations between sleep and intellectual ability on the trait-level. Behaviorally, sleep duration was negatively related to intellectual ability, whereas different measures of chronotype were not related to intellectual ability. Physiologically, several variables derived from the sleep EEG were also related to intellectual ability. Power within specific frequency bands including the alpha, sigma and beta range and individual sigma power were positively related to intellectual ability, in particular to full scale IQ, fluid IQ and working memory. Third, the relationship between specific variables of the sleep EEG and intellectual ability is not only a global phenomenon, but also involves local aspects. Correlations between sleep EEG power and intellectual ability showed a specific topographical pattern.

Taken together, these studies indicate, that sleep may be considered a trait, and a behavioral and physiological correlate of intellectual ability in healthy children.

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# I Introduction

## 1.1 The phenomenon of sleep

Sleep is a behavioral state which covers a large part of everyone's life. Sleep is also a focus of interest for many scientific disciplines such as medicine and psychology and bears substantial relevance for the entire society. For example, sleep deprivation and chronic sleep restriction is known to impair the performance of individuals, their health and well–being (Banks & Dinges, 2007; Carskadon, 2004). In addition to the different disciplines involved in sleep research (e.g., sleep medicine, psychology, etc.), there are also different levels – from molecular research on genetic polymorphisms influencing the response to sleep deprivation (Landolt, 2008) to cognitive, emotional and behavioral consequences of altered or restricted sleep on the systems' level (Durmer & Dinges, 2005; Pilcher & Huffcutt, 1996).

Despite the fact that sleep is highlighted from many disciplines and described in many facets, it is still not known, why we have to sleep. From animals to human beings, it is well-established that sleep is indispensable to life - continuous sleep-restriction has ultimately lethal effects (see Bonnet, 1994). A number of hypotheses have been proposed to explain the functions of sleep. For example, sleep may serve neuropsychological functioning such as memory consolidation and learning (Walker, 2009). On the cellular or molecular level, it has been suggested that sleep represents a possible mechanism for the facilitation of brain plasticity (Dang-Vu, Desseilles, Peigneux, & Maquet, 2006; Frank, Issa, & Stryker, 2001; Tononi & Cirelli, 2006). Even though the precise role and differential influence of certain sleep stages for cognitive performance as well as the involved mechanism are still debated (Diekelmann & Born, 2010) there is a general consensus - Sleep influences cognitive functioning. Among others, sleep deprivation impairs cognitive performance, with a particular susceptibility of those neurocognitive domains that mainly rely on the frontal cortex, such as executive functions and working memory (Durmer & Dinges, 2005; Horne, 1993; Jones & Harrison, 2001). Yet, sleep may also have beneficial effects on cognitive functioning (see below).

On the other hand cognitive processes of the waking brain also have an impact on sleep. For instance, activation of circumscribed brain areas with a visuomotor

learning task resulted in a local increase of slow-wave activity (SWA or delta power, corresponding to spectral power of the sleep electroencephalogram (EEG) in the range of 0.75 to 4.5Hz) of non-rapid-eye-movement (NREM) sleep during the initial phase of the subsequent night. This local increase of SWA was located above those brain areas which were previously challenged (Huber, Ghilardi, Massimini, & Tononi, 2004). Along the same lines, there is also evidence that sleep facilitates long-lasting changes in the representation of memories: Comparing recall performance after sleep to those after sleep deprivation respectively, additional connectivity in the sleep condition was observed for the medial prefrontal cortex in a study using functional magnetic resonance imaging (fMRI). Six month after the learning session, cortical activation was still different for participants who initially slept after the learning session compared to those who did not (Gais et al., 2007).

### 1.1.1 Physiological aspects

Sleep is characterized by an increased threshold of arousal, but also by distinct electrophysiological and metabolical changes within the brain (Benington & Heller, 1995) and the body (Tasali, Leproult, Ehrmann, & Van Cauter, 2008). About 5% of brain genes expressed in the neocortex are known to change their level of expression depending on the actual behavioral state (Cirelli, 2005).

With the application of electroencephalography (EEG) as a tool to study the sleeping brain, it has been discovered that sleep is not a passive state. In contrast to earlier assumptions, the brain is in fact highly active during sleep (Aserinsky & Kleitman, 1953). As already reported by Moruzzi and Magoun (1949), the EEG during sleep is characterized by high-voltage slow waves, which are, in the transition to wakefulness, abolished by stimulation of the brain stem reticular formation. This stimulation evokes changes resulting in a desynchronization of the EEG, characterized by low-voltage fast activity (Moruzzi & Magoun, 1949). Polysomnography (PSG) which is considered the 'gold standard' method for the assessment of sleep allows for a distinction of different behavioral states: wakefulness (W), rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep. NREM sleep can further be subdivided in stages N1, N2, and N3 (see Iber, Ancoli-Israel, Chesson, & Quan, 2007), which are characterized by distinct physiological features and graphoelements (see also 1.2 Assessment of sleep, 1.2.4 Polysomnography). NREM sleep is characterized

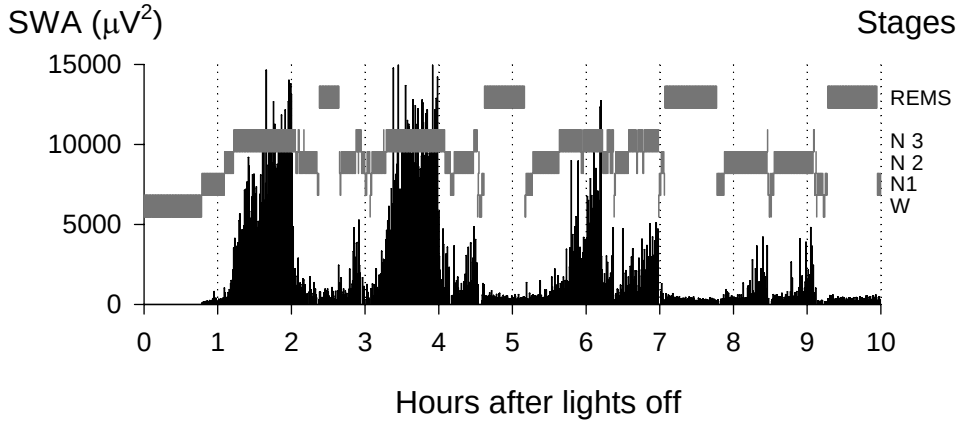
by the presence of slow-waves (usually defined as peak-to-peak amplitude > 75μV and frequency < 2Hz) and sleep spindles, involving short waxing and waning synchronous bursts of activity (usually defined as graphoelements with a frequency between 12 and 15Hz). REM sleep exhibits a mixed frequency, low voltage pattern (similar to the waking EEG), bursts of rapid-eye-movements and a loss of muscle tone.

Sleep and wakefulness are associated with neuronal activity in defined anatomical structures and controlled by specific neurotransmitters. During wakefulness, noradrenergic neurons in the locus coeruleus, serotonergic neurons in the dorsal raphé nucleus and histaminergic neurons in the tuberomammillary nucleus provide arousing input to various forebrain regions such as the diencephalon, limbic telencephalon and the neocortex. This input is in turn regulated by hypochretin/orexin neurons in the perifornical area of the lateral hypothalamic area. The cholinergic brain system, which originates in the brain stem and projects to thalamocortical nuclei and the reticular nucleus of the thalamus ("ascending reticular activating system", ARAS), is another key component of waking behavior. Neurons in these arousing systems fire rapidly during wakefulness, but fire considerably less during NREM and REM sleep. The inhibition of these wakefulness promoting systems is mediated by the ventrolateral preoptic nucleus (VLPO), primarily containing GABAergic neurons. The VLPO and the ARAS interact mutually inhibitory and thus represent a "flip-flop" mechanism. The "flip-flop" mechanism suggests that discrete behavioral states with sharp transitions (either sleep or wakefulness) are induced instead of intermediated states. It is further assumed that the VLPO consists of specialized sub-regions, some of them responsible for the generation of NREM sleep and others responsible for the generation of REM sleep (for review on the neuroanatomic regulation of sleep and wakefulness see Saper, Chou, & Scammell, 2001; Saper, Scammell, & Lu, 2005; Szymusiak & McGinty, 2008).

Sleep is characterized by a cyclic nature, alternating between NREM and REM sleep phases. After sleep onset, a progression from N1 to N2 and N3 occurs, which is followed by a subsequent progression back to N1 and the first occurrence of REM sleep. In adults, the normal cycle length lasts approximately 90 to 100 minutes, with REM sleep accounting for approximately 20 to 25% of the total sleep time (Dement & Kleitman, 1957). In children, the normal cycle length is shorter (approximately 50 to 60 minutes during early infancy (Jenni,

Borbély, & Achermann, 2004) and approximately 50 to 110 minutes in preschool children (Bes, Schulz, Navelet, & Salzarulo, 1991)). Thus, sleep exhibits an ultradian rhythm (cyclic pattern repeated throughout a period, less than 24 hours) of alternating NREM and REM sleep phases (see fig. 1).

Figure 1: Sleep profile or hypnogram (grey bars) and SWA pattern (black lines) across the night. Example of one female subject, age 10 years.




Sleep onset, duration and structure are primarily regulated by two separate processes, which were described in the *two process model of sleep regulation*, formulated first by Borbély (1982). According to the model, which has, among others be refined and further specified by Daan and colleagues (Daan, Beersma, & Borbély, 1984) one process (process S) is a function of prior sleep and wakefulness, that is accumulates during wakefulness and declines during subsequent sleep, and thus reflects a homeostatic component of sleep regulation. The other process (process C) is controlled by a sleep-independent circadian process (cyclic pattern, repeated approximately once throughout a 24-h day). The interaction between process S and process C determines the timing of sleep and wake. Sleep propensity is determined by the combined action of both processes (Borbély, 1982; Daan, Beersma, & Borbély, 1984). The interaction of the homeostatic and the circadian process accounts for example for the fact that wakefulness can be maintained throughout the day even though sleep need is

continuously rising in the course of the time being awake (Edgar, Dement, & Fuller, 1993). Albeit a slight dip in alertness is usually experienced around noon, wakefulness can be maintained to the evening with only minor fluctuations in daytime behavioral performance.

According to the two process model of sleep regulation, process S can be described as exponential function of slow-wave activity (SWA or delta power, corresponding spectral power of the sleep EEG in the range of 0.75 to 4.5Hz) of NREM sleep by a declining trend across the night and across the individual sleep episode (see fig. 1)

Notably, sleep intensity, measured as the changes in SWA or delta power, is homeostatically regulated, rather than the duration of sleep per se. Following sleep deprivation, delta power is increased (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Webb & Agnew, 1971), whereas napping reduces delta power in the following night (Feinberg, Fein, & Floyd, 1980; Werth, Dijk, Achermann, & Borbély, 1996). On the behavioral level, sleep latency has frequently been used as a marker for sleep pressure, which can for example be determined by the *multiple sleep latency test* (Carskadon & Dement, 1979; Carskadon et al., 1986). Usually, the investigation of process S involves partial or total sleep restriction protocols, whereas the circadian component of sleep regulation (process C) and the interaction between process S and process C can be examined with the use of constant routine or forced desynchrony protocols (see e.g., Dijk & Czeisler, 1995).

The circadian component of sleep regulation (process C), which oscillates with a period of about 24h is, under normal conditions, entrained by external Zeitgebers. These are stimuli such as daylight, temperature, or social clues which normally help to entrain the internal clock to a 24-h rhythm. In the absence of external Zeitgebers, the endogenous, free-running circadian rhythm, runs in fact a bit longer than 24-h and becomes more and more desynchronized (see Foster & Kreitzman, 2005). Notably, exposure to light has been identified as the dominant Zeitgeber for entrainment (Duffy, Kronauer, & Czeisler, 1996), even showing a dose-response relationship (Boivin, Duffy, Kronauer, & Czeisler, 1996). Whereas the anatomical substrate for process S is still unknown, process C is controlled by a distinct brain structure, the nuclei suprachiasmatici (SCNs) (for review see Moore, Speh, & Leak, 2002). Many physiological markers such as body temperature, blood pressure and plasma level of hormones such as cortisol

or melatonin are subject to circadian influences and characterized by a specific time course (Born & Fehm, 1998; Brown et al., 2008). The time course of these circadian markers is closely related to process C, the circadian component of sleep regulation. For example, sleep latency is shortest when the body temperature is close to its minimum (Dijk & Czeisler, 1995).

In sum, sleep is a highly regulated process, influenced by a homeostatic sleep-wake-dependent (process S) and a circadian sleep-wake-independent (process C) process. In addition to these physiological aspects of sleep regulation, there are also socio-cultural, psychological, and developmental aspects relevant to the understanding of the phenomenon of sleep.

### 1.1.2 Psychological aspects

Psychiatric diseases are characterized by psychological and behavioral problems, but often also involve alterations regarding the sleep pattern (Abad & Guilleminault, 2005; Haba-Rubio, 2005; Krahn, 2005). For example, three quarters of patients with major depression suffer from insomnia, whereas others are rather affected by hypersomnia (Nutt, Wilson, & Paterson, 2008). With longitudinal studies, the formally bidirectional association between sleep disorders (in particular insomnia) and depression could be clarified: Insomnia has been identified as a risk factor for a first-time onset as well as for the recurrence of a major depression (Franzen & Buysse, 2008). Recently, the sleep EEG has even been suggested as a potential biomarker for the diagnosis of depression as well as a tool for evaluating the efficiency of therapeutic interventions (Steiger & Kimura, 2010). Besides psychiatric diseases, several other somatic or neurological conditions which affect the integrity of the central nervous system are known to alter the sleep pattern, behavior and EEG. For example, neurodegenerative processes such as Alzheimers' and Creuzfeld Jacobs' disease (Petit, Gagnon, Fantini, Ferini-Strambi, & Montplaisir, 2004) or ischemic events (Bassetti & Aldrich, 2001; Gottselig, Bassetti, & Achermann, 2002) feature changes in sleep behavior and the sleep EEG.

However, sleep does also play an important role for the psychological well-being in non-clinical populations. A bidirectional relationship between good sleep, positive affect and psychological well-being has been reported (Steptoe, O'Donnell, Marmot, & Wardle, 2008), reflecting personal experience and common sense. Specifically, sleep duration per se does not correlate with quality of well-

being, but self-reported satisfaction with sleep does (Jean-Louis, Kripke, & Ancoli-Israel, 2000). Thus, general assumptions and beliefs about sleep are sometimes misleading, and may eventually evoke problems that did originally not exist. For instance, it could be demonstrated that sleep factors such as sleep duration and tiredness accounted for only a small proportion of variance of objectively assessed cognitive test scores in healthy adults, but for a much larger proportion of the variance in subjective cognitive functioning. Moreover, when adjusting for sociodemographic variables, the association between sleep factors and cognitive functioning was no longer present (Kronholm et al., 2009).

### 1.1.3 Developmental aspects

Sleep changes substantially during development, in particular early in life. These changes occur on the physiological as well as on the psychological level and involve quantitative and qualitative aspects. For example, sleep duration is known to decrease in the course of childhood (from more than 50% of the 24-h day in the newborn (Iglowstein, Jenni, Molinari, & Largo, 2003) to approximately 7 to 7 ½ per 24 hours in adults (Jean-Louis, Kripke, & Ancoli-Israel, 2000; Kronholm et al., 2008; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004)). This decline in sleep duration is paralleled by the following alterations of the sleep structure: a gradual change from a poly- to a monophasic sleep pattern (Anders, Sadeh, & Appareddy, 1995), a decrease in REM sleep compared to NREM sleep (Coons & Guilleminault, 1982), and distinct changes in sleep EEG power and the power within specific frequency bands of the sleep EEG (Jenni & Carskadon, 2004; Tarokh & Carskadon, 2010). The topographical distribution of the sleep EEG power also varies with age (Findji, Catani, & Liard, 1981; Jenni, Achermann, & Carskadon, 2005; Kurth, Ringli et al., 2010). For instance, recent cross-sectional findings suggest that SWA shifts from posterior to anterior regions (Kurth, Ringli et al., 2010) which may parallel developmental changes in brain morphology, with brain regions that are associated with basic sensory or motor functions maturing first, followed by those involved in more complex behavior and cognitive functions (for review see Casey, Tottenham, Liston, & Durston, 2005). In particular, the maturation of the frontal lobe is known to follow a specific time course, characterized by a preadolescent increase followed by a postadolescent decrease in cortical grey matter (Shaw et al., 2006; Sowell et al., 2004). Both, the time course of synaptic density (Giedd et al., 1999;

Huttenlocher, 1979) and SWA (Campbell & Feinberg, 2009; Feinberg, 1982) follow an inverted U-shaped time course. This striking similarity has led to the assumption that SWA reflects cortical maturation and plasticity during development (Buchmann et al., 2010; Campbell & Feinberg, 2009; Feinberg & Campbell, 2010; Kurth, Ringli et al., 2010). Because these age-related changes are highly specific for sleep physiology as well for brain morphology and thus for cognitive development, it may be suggested that common underlying processes are involved.

Developmental changes of sleep are, however, not only relevant from a descriptive point of view, but have also psychological and behavioral implications. For example, parasomnias such as night terrors are relatively transient phenomena, with age-dependent prevalence, onset and disappearance, emerging during the first decade of life and usually disappearing thereafter (Laberge, Tremblay, Vitaro, & Montplaisir, 2000). Moreover, the timing of sleep and wakefulness, i.e. the circadian sleep regulation, considerably changes during development, which is most prominent during early infancy and puberty (see Jenni & LeBourgeois, 2006). For example, circadian phase markers such as melatonin are known to shift dramatically during puberty, which is probably accounting for the adolescents' tendency to stay up late and sleep in later (Carskadon, Acebo, & Jenni, 2004). This behavioral peculiarity of the adolescent's sleep may however clash with the start of school and other societal demands (Jenni & LeBourgeois, 2006). Prepubertal children are in turn often affected from parental expectations about children's sleep behavior - regarding sleep start, sleep duration and sleep end. Children expected to sleep and stay in bed significantly longer then their actual sleep need, will finally be affected by insomnia and frequent awakenings, which in turns aggravates the vicious cycle (Jenni & O'Connor, 2005). Expectations about children's sleep behavior may create serious problems for the child, the parents themselves and the child-parent-interaction, when not met by the child's actual behavior (Sadeh & Anders, 1993). Thus, a misfit between parental expectations, culturally normative bedtime practice and individual characteristics of the child (e.g., endogenous components such as sleep need or chronotype) may be at the bottom of children's problematic sleep behavior (Jenni & O'Connor, 2005). In preschool children, up to 25-40% are affected by insomnia, bedtime resistance and disruptive nighttime awakenings (Ivanenko & Gururaj, 2009), illustrating the

relevance and prevalence of psychosocial issues in sleep research. Thus, sleep regulation and behavior which is subject to considerably maturational change, is not only a scientific matter, but also encompasses major societal, clinical and psychosocial implications.

## 1.2 Assessment of sleep – behavioral, psychological and physiological variables

There are several possibilities to assess quantitative and qualitative aspects of sleep, methods suitable for the evaluation of objective and subjective characteristics of sleep. Each of these methods can be described by its pros and cons and may be appropriate to a certain context.

### 1.2.1 Questionnaires

Questionnaires are an elegant tool for data collection - they are easy to administer and analyze, cheap and non-invasive (Eaden, Mayberry, & Mayberry, 1999). They can be applied to examine specific hypothesis in an experimental context, but also as a broad screening tool in epidemiological research. There are self-rating questionnaires for different clinical purposes, e.g., the Sleep Disorders Questionnaire (SDQ) for the assessment of psychiatric sleep disorders, apnea and narcolepsy (Douglass et al., 1994), but there are also questionnaires developed for assessment-by-others. These assessments-by-others offer the possibility to collect information about a third person – a person who is not able to answer or unaware of the matter of question. Parent-ratings, for example the Sleep Disturbance Scale for Children (SDSC, Bruni et al., 1996) are a convenient way of collecting data on children's behavior. For a review of questionnaires for different sleep related aspects and purposes see Lomeli et al. (2008).

Despite many advantages, there are, however, also a number of drawbacks with the use of questionnaires (see Stone, 1993). For example, the validity and reliability strongly depends on the subject's compliance and actual knowledge. Moreover, agreement between self-rating and the assessment-by-others may be poor. When parents are asked about their children's behavior, they may or may not honestly answer the questions, and they may even ignore the child's actual situation. An epidemiologic study from Finland has, for instance, demonstrated that the correspondence between 8-9 year old children and their parents was poor when assessing sleep problems (Paavonen et al., 2000). In contrast to this epidemiologic survey on clinical aspects of sleep behavior, questionnaires may nevertheless be an appropriate and convenient tool to investigate the normal sleep behavior in healthy children.

Most questionnaires for the assessment of children's sleep behavior, such as the Pediatric Sleep Questionnaire (PSQ, Chervin, Hedger, Dillon, & Pituch, 2000), the

Sleep Disturbance Scale for Children (SDSC, Bruni et al., 1996) or the Children's Sleep Habits Questionnaire (CSHQ, Owens, Spirito, & McGuinn, 2000) focus on problematic or pathologic sleep behavior. For example, the CSHQ (Owens, Spirito, & McGuinn, 2000), a parent-report screening survey for school-age children is based on common clinical symptoms and diagnoses of the Pediatric International Classification of Sleep Disorders (Thorpy, 1990). Studies of the present thesis investigated, however, a normal population of healthy prepubertal children. Thus, none of the earlier mentioned questionnaires appeared suitable for this non-clinical population. Therefore, the Children's ChronoType Questionnaire (CCTQ, Werner, Lebourgeois, Geiger, & Jenni, 2009), a tool for the collection of qualitative and quantitative data in non-clinical populations of healthy children was administered. Besides, the Pediatric Daytime Sleepiness Scale (PDSS, Drake et al., 2003) was applied to control for a possible bias resulting from excessive daytime sleepiness. Questionnaires, used by studies performed for the present thesis are attached (see Appendix).

The CCTQ (Werner, Lebourgeois, Geiger, & Jenni, 2009) is a parent-report mixed-format questionnaire which allows for a calculation of the individual sleep duration, separately for week-days, weekend days and free days and asks for information on napping behavior. Besides, multiple measures of chronotype are obtained. Chronotype is a trait-like individual characteristic (Kerkhof, 1985), "a spectrum of individual variations in timing of activity preference" (Tankova, Adan, & Buela-Casal, 1994 , p.672). Whereas some people prefer to get-up early and have their general performance optimum in the early hours of the day (usually named morning types or metaphorically speaking "larks"), others prefer to get-up late, but also stay up late and have their general performance optimum in the late hours of the day (usually named evening types or metaphorically speaking "owls", Tankova, Adan, & Buela-Casal, 1994). Chronotype represents an individual characteristic that influences sleep and waking behavior, which is closely linked to physiological variables. For instance, it has been reported that morning types have earlier sleep schedule (Carskadon, Vieira, & Acebo, 1993), but also earlier secretion of melatonin (Laberge et al., 2000). For a detailed description and discussion on children's chronotype and the CCTQ see II Empirical work, study II.

The PDSS (Drake et al., 2003) is a self-report questionnaire for children, designed to assess sleepiness in non-clinical populations. Daytime sleepiness is

the "difficulty in maintaining a desired level of wakefulness" (Young, 2004). Excessive daytime sleepiness may have severe consequences on health and safety, but may also influence daytime cognitive performance (Young, 2004). The PDSS sum score is calculated on 5-point Likert-scale of eight different items, which describe specific situations during the day, for example: "How often do you have the feeling that you would need more sleep?"

### 1.2.2 Actigraphy

Actigraphy is a method for the continuous monitoring of physical activity and rest periods via a wristwatch-like device containing a sensor that records omnidirectional acceleration. Based on the assumption that the activity counts recorded by the actigraph reflect sleep-wake behavior, actigraphy represents a convenient tool to derive various sleep variables such as sleep latency and duration, wake after sleep onset, and sleep efficiency (defined as sleep time per time in bed). It is a suitable, cheap and accurate method to assess sleep behavior and distinguish between clinical groups (Sadeh & Acebo, 2002). A major advantage of actigraphy is the possibility to assess rest behavior at subject's home. Home monitoring allows for investigations on a large number of subjects, or over a prolonged period of time. Furthermore, actigraphy offers the possibility to investigate clinical populations or younger children – research otherwise not viable in the laboratory environment. Finally, it can be assumed that home monitoring has only minor influence on subject's normal sleep behavior, thus optimizing compliance and quality of data with this non-invasive method.

Usually, several days are recorded, with software packages offering applications for different purposes, such as the actogram (see fig. 2), the sleep-wake display or analysis tools for clinical purposes, e.g., for the quantification of periodic limb movements. Despite the large amount of options for recording devices and analysis software, there is, however, no general consensus about the algorithm of data analysis to use. Moreover, validity has not been established for all available devices or clinical groups (Sadeh & Acebo, 2002) and there is some evidence that actigraphy may not be a valid method for identifying infant sleep and wake (Insana, Gozal, & Montgomery-Downs, 2010). Besides, the sensitivity threshold of the device cannot be optimal for each situation: An epoch where somebody is turning rigorously while being asleep may be scored as wake,

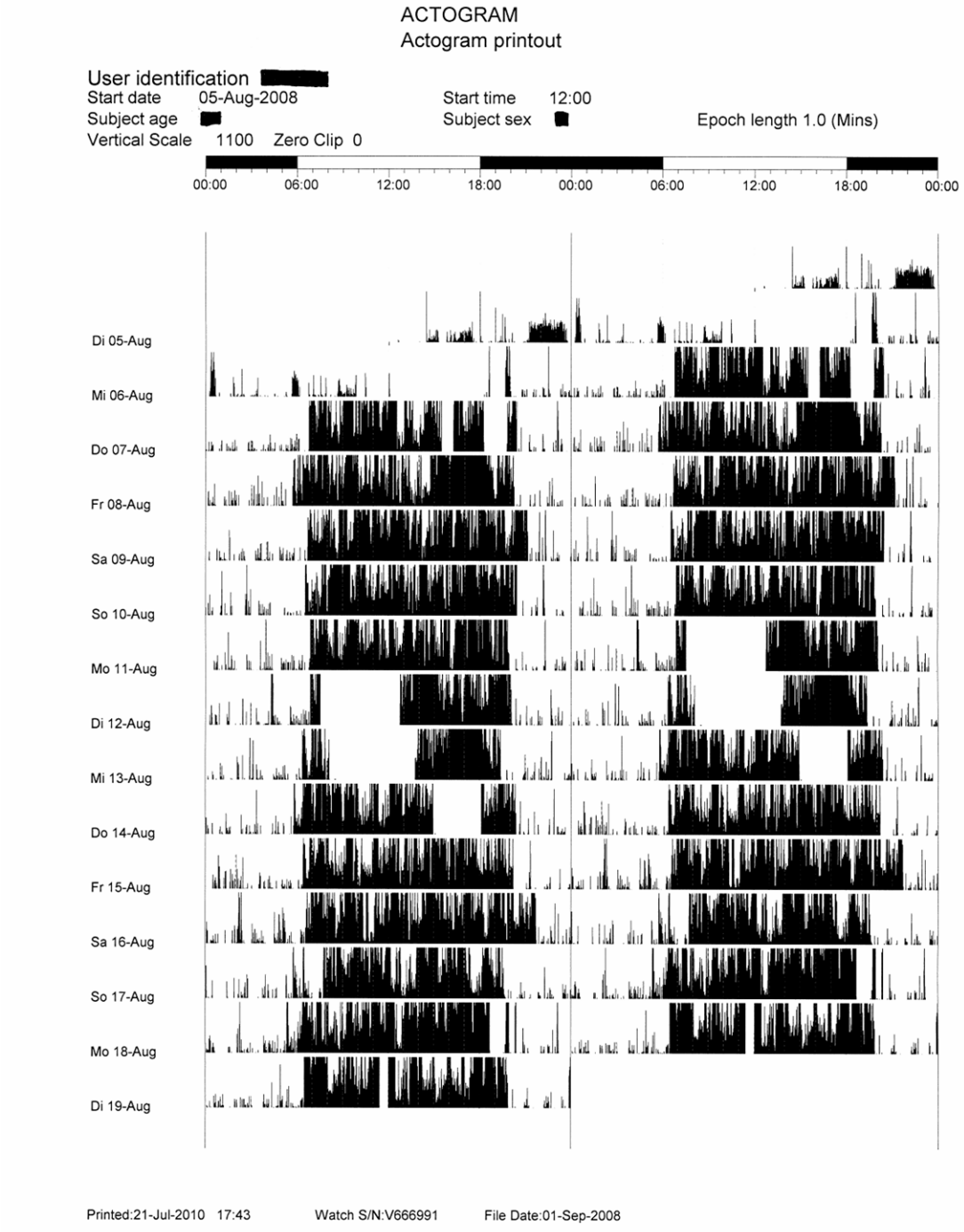
whereas an epoch of quiet wakefulness may be mistaken as a sleep episode. Apart from artifacts originating from the device, there are also potential artifacts arising from the subject - external movements will be mistaken as subject's own activity. For example, infants carried around while being asleep or the activity of somebody bed-sharing with the subject will obviously bias the assessment. Along the same lines, misinterpretation can easily result from the removal of the actigraph; whenever the device is taken off, the actigraph will misleadingly identify these epochs as sleep.

Despite these limitations and shortcoming of actigraphy, there are, however, a number of strategies in order to optimize data collection and minimize artifacts. In general, the higher the number of recording days, the better the quality of data. For the assessment of sleep duration, a minimum number of seven days of recording is recommended (Acebo et al., 1999). To avoid external movements picked up by the actigraph and the misinterpretation resulting from not-worn actigraphs, a detailed protocol is essential (Acebo & LeBourgeois, 2006). The protocol does not only help in the data analysis, it may also justify decisions about the exclusion of recording days from the analysis. Finally, one should be very strict and clear in defining exclusion criteria, be aware of the given research questions and carefully pay attention to the potential artifacts that may occur within the particular paradigm/experimental protocol or population. For example, when actigraphy is used as a control for subject's compliance to a given experimental protocol, is has a different purpose than in a clinical context, when used in an evaluation study on drug effects on the sleep-wake cycle. When applying actigraphy, one should ask several questions, such as: Does it matter if the subject is sick during the recording? Does is matter if bed-sharing occurs? Does it matter if the subject consumes alcohol or is on medication during recording? Questions like these should either be incorporated in the exclusion criteria or at least been recorded in the concomitant protocol.

In summary, when carefully paying attention to these avoidable pitfalls and with the application of a concomitant protocol, actigraphy represents a suitable, cheap and accurate method to assess rest-activity-behavior - at least for certain populations and certain devices.

Figure 2: Example of an actogram (one female subject, age 10 years), 14 days of continuous home monitoring, recorded with 1-minute sampling rate and evaluated by medium sensitivity.

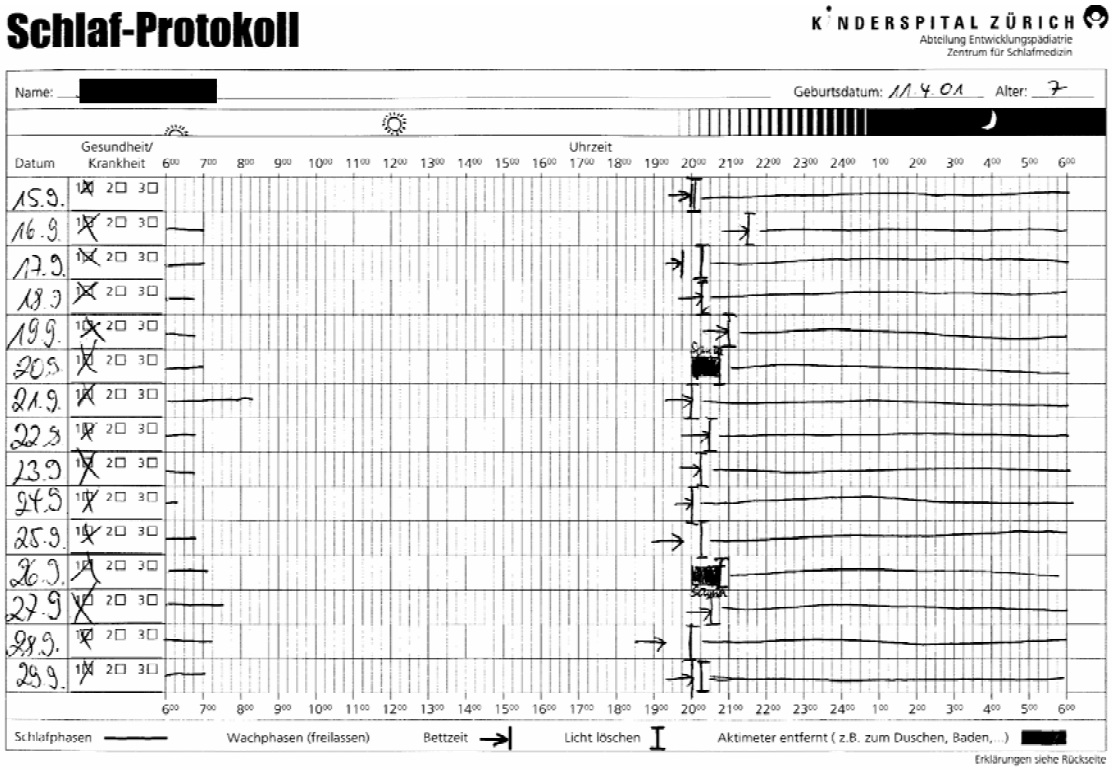
Note the dominance of activity counts (black bars) during daytime and its relative absence during nighttime. Bare areas (no activity counts for several consecutive minutes) indicate that the device has been removed.



1.2.3 Diary

Sleep diaries or logs are used as instruments to control for subject's compliance during experimental protocols or independently as an assessment tool for sleep behavior. For scientific purposes, diaries are mainly used as an additional source of information, e.g., to optimize validity of actigraphically assessed sleep variables. For clinical practice, they may also be applied as an exclusive assessment tool. Sleep variables such as bed time, time of lights off, get-up time and wake time after sleep onset can easily and directly be assessed by diaries (see fig. 3).

Figure 3: Sleep diary used for the studies performed during the present thesis. Modified version of the sleep diary that is used for clinical practice and consulting at the Children's University Hospital of Zurich (see Appendix). The adaptations were made to better fit the characteristics of the study population and to address the specific research questions. Example of one male subject, age 7 years).



These variables in turn can be used to calculate further sleep related variables, such as the individual sleep duration. The sleep dairy can also illustrate a person's sleep behavior in general (e.g., variability of sleep timing during the week compared to the week-end) and provide information about a person's sleep phase preference, by calculating the mid-sleep point. The mid-sleep point is computed as the mid point of the sleep period - half of the sleep duration added to the sleep start. Sleep dairies are cheap and easy to apply, thus represent a convenient method to adequately assess sleep start, sleep end, and assumed sleep time (see Werner, Molinari, Guyer, & Jenni, 2008). For scientific purpose, it may, however, be necessary to use other methods in addition to sleep diaries.

### 1.2.4 Polysomnography

Polysomnography (PSG) is based on simultaneous recordings of physiological variables such as the electroencephalogram (EEG), the electrooculogram (EOG) and the electromyogram (EMG). The pattern of EMG and EOG activity, together with the frequency, amplitude and waveform of the EEG provides the basis for subsequent scoring of sleep stages (assigned for 20- or 30-s epochs), and calculation of sleep variables, such as the total sleep time or sleep latency (Iber, Ancoli-Israel, Chesson, & Quan, 2007; Rechtschaffen & Kales, 1968).

The EEG signal which is usually recorded with scalp electrodes results from populations of simultaneously active neurons - it represents the sum of postsynaptic potentials, mainly originating from pyramidal cells. During NREM sleep, the synaptic potentials are synchronized, representing characteristic oscillatory pattern (Buzsaki & Draguhn, 2004), e.g., slow waves.

Wakefulness is characterized by high muscle tone, rapid-eye-movements, and high frequency, low voltage EEG activity - mainly alpha activity (spectral power in the range of 8 to 12 Hz) during relaxed wakefulness and beta/gamma activity (spectral power > 20 Hz).

Rapid-eye-movement (REM) sleep, also called "paradoxical sleep", shows a similar EEG pattern compared to the waking state, but a very low muscle tone and bursts of phasic rapid-eye-movements.

In the latest scoring manual of the American Academy of Sleep Medicine (see Iber, Ancoli-Israel, Chesson, & Quan, 2007), non-rapid-eye movement (NREM) sleep consists of three separate stages, N1 to N3, with N3 replacing and combining NREM sleep stage 3 and 4 (corresponds to slow wave sleep (SWS) of

the earlier Rechtschaffen and Kales (1968) nomenclature). N1 can be described as a transitional stage between wakefulness and sleep, characterized by relative high frequency, low voltage EEG activity (less than 50% of alpha activity), slow rolling eye movements and reduced EMG amplitude. N2 is characterized by an absence of eye movements, a low muscle tone and specific EEG graphoelements, such as K-complexes and sleep spindles. N3 is characterized by an absence of eye movements, low muscle tone and low frequency, but high voltage EEG activity, mainly delta (spectral power in the range 0.75 to 4.5 Hz) and theta (spectral power in the range 4.5 to 8 Hz) activity.

Finally, with the application of a mathematical algorithm, the Fast Fourrier Transformation (FFT, Cooley & Tukey, 1965), the sleep EEG can be quantified and decomposed into its constituent frequency components. The FFT transforms the EEG signal from the time domain to the frequency domain, resulting in a power density spectrum which is expressed as power per bandwidth (see fig. 4).

Using multiple EEG electrodes, for instance 128 electrodes high density EEG (see fig. 5) instead of the classical configuration (EEG derivations C3A2 or C4A1, EOG and EMG) (see Rechtschaffen & Kales, 1968), the higher spatial resolution offers the possibility to analyze also local distribution of spectral power and the topographical pattern.

Figure 4: Two examples of mean all-night power density spectra (gray line: subject LH (male, 9.5 years old), black line: subject RC (male, 10.6 years old). Power density spectrum of NREM sleep (left panel) and power density spectrum of REM sleep (right panel).

Note the dominant peak in the NREM sleep power density spectrum (left panel) in the sleep spindle frequency range (spindle frequency activity (SFA): 12-15Hz).

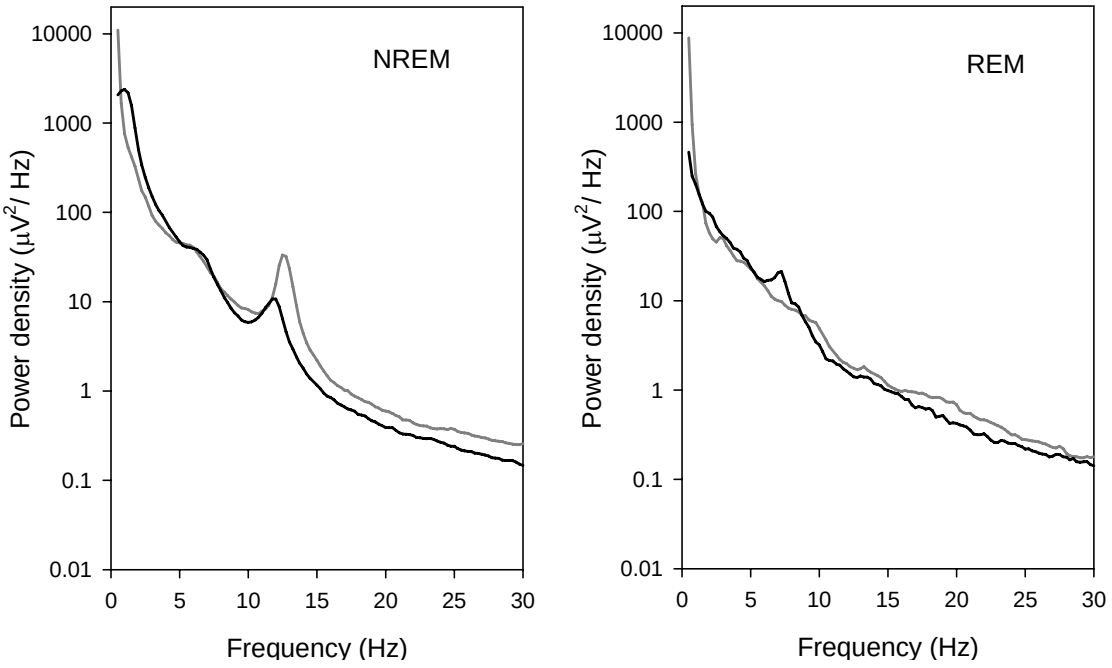


Figure 5: Electrode placement of the 128-electrode high-density EEG system (Geodesic®) used for studies performed during this thesis.

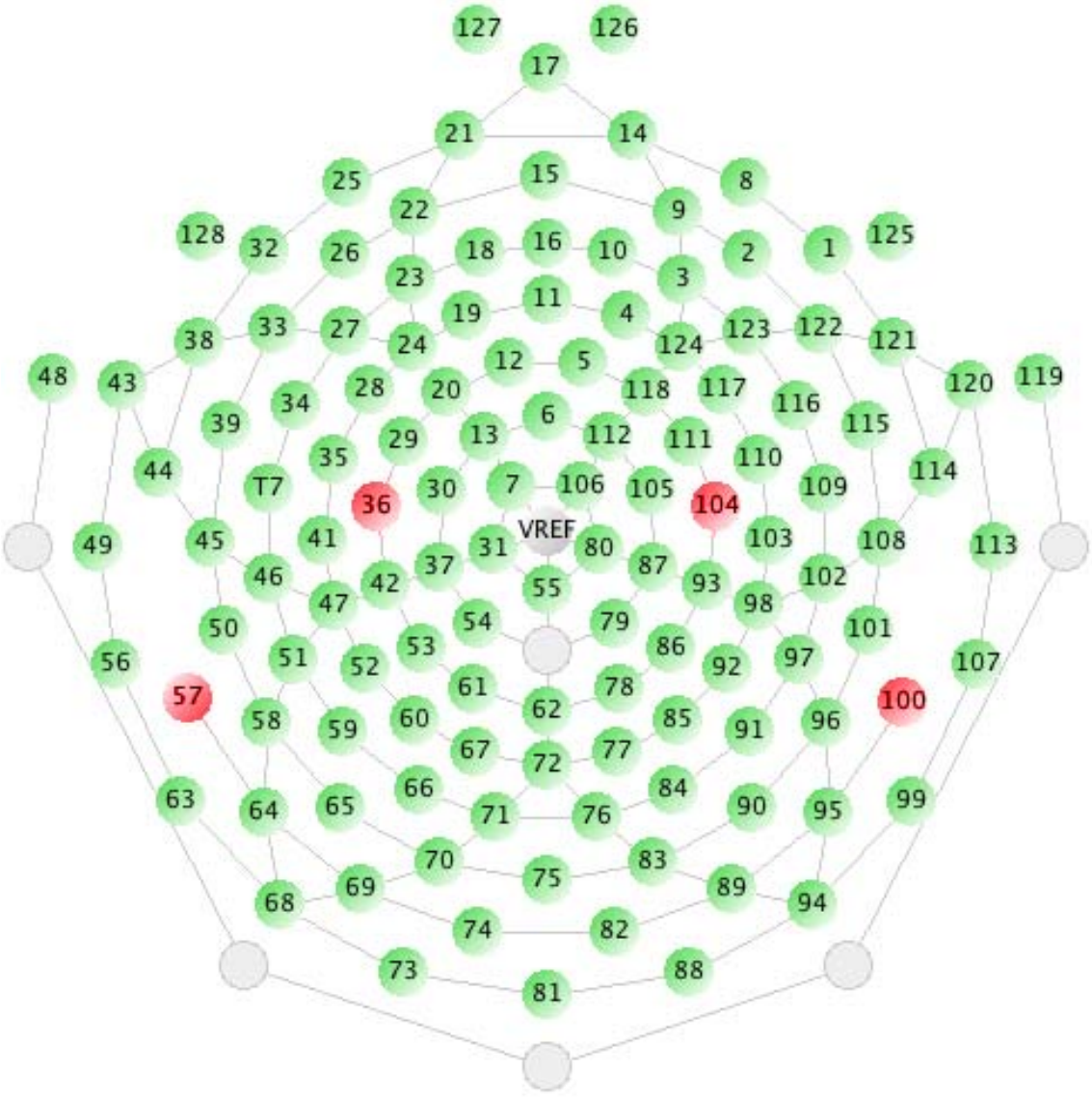
C3: electrode no. 36

C4: electrode no. 104

A1: electrode no. 100

A2: electrode no. 57

VREF: vertex reference, predefined reference electrode



### 1.3 Cognition, learning and intelligence – concepts and definitions

Evolving from different schools of thought and research traditions, cognition and intelligence have been unrelated terms for a long time, but simultaneously been used as synonyms. Cognition can be described as basic information processing, the application of knowledge and distinct cognitive processes, whereas intelligence relates to individual differences in mental ability, conceptualized as a general factor, the so-called g-factor (Spearman, 1904, 1923). Thus, cognitive psychologists were primarily interested in "lower-order" processes of the mind, whereas the study of individual differences in intelligence examined "higher-order" and metacognitive abilities (Pretz & Sternberg, 2005). As such, "learning" may be considered as an example of a single cognitive process on a lower-order level. According to Baddeley, "the term *learning* can be legitimately used for … remembering a personal incident, acquiring new information, mastering a new skill, or developing a new habit" (Baddeley, 1999).

Including a developmental perspective, Anderson highlighted another important aspect which at the same time offers an elegant way to differentiate between the two concepts cognition and intelligence: cognitive processes are subjected to an age-dependent performance increase (on a quantitative and qualitative level), whereas intelligence refers to individual differences that remain constant across development (Anderson, 2005).

Despite these inherent conceptual differences between bottom-up (based on "lower-order" cognitive processes) and top-down approaches (related to "higher-order" intellectual ability), there is, however, a vagueness of definitions and terminology which deserves clarification. It is essential to differentiate between two concepts: Intelligence is conceptualized as a *trait*, whereas cognitive processes are conceived as *state*-dependent. In general, a trait represents a behavioral or biological disposition which is empirically or statistically established (Allport, 1931), not specific to certain situations or tasks and fairly stable over time. Intelligence is characterized by a high long-term intra-individual stability (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Moffitt, Caspi, Harkness, & Silva, 1993), with stability coefficients for general intelligence ranging from .89 to .96 (Hertzog & Schaie, 1986). Furthermore, based on comparisons in mono- versus dizygotic twins, a considerably large genetic foundation of intelligence was reported (Deary, Johnson, & Houlihan, 2009), with heritability estimates of

40-50% during childhood and 80% in adulthood (Baltes, Staudinger, & Lindenberger, 1999). Overall, intelligence fits the general definition of a trait on the psychological and biological level. In contrast, cognitive processes, such as the performance in a perceptual motor learning task or a verbal learning paradigm are characterized by situational fluctuations and may therefore be considered as *state*-dependent.

Although (higher-order) intelligence and (lower-order) cognitive processes are mutually depended and influenced by each other, there is an important distinction: Whereas cognitive processes are influenced by the underlying trait intelligence as well as by additional external and internal factors (e.g., the current setting, intrinsic motivation, level of concentration, alertness, etc.), intelligence should covary with lower-order cognitive processes, but not basically with situational factors.

The term "intelligence" has been used by several disciplines (e.g., psychology, behaviorism, computer science) and in different contexts (e.g., emotional, practical and social intelligence, see Weber & Westmeyer, 2001). However, most research in the field of intelligence has been related to what can be described as „academic intelligence". "Intelligence, by definition, is what intelligence tests measure" (Jensen, 1972). This prominent definition, circular in nature and unhelpful in specifying the subject matter, is nevertheless worth keeping in mind because it is making the point that performance in a given test always depends on the underlying concept and assessment tool. Other definitions link intelligence to overt intelligent behavior, for instance intelligence as "the ensemble of abilities which is common to all successful individuals of a given culture" (Hofstaetter, 1957). Although there may be as many definitions of intelligence as there are researchers working in the field, there nevertheless exists a certain consensus on which most would agree: Intelligence is an umbrella term for adaptive behavior, for the ability to reason or to solve problems (Gottfredson, 1997).

## 1.4 Assessment of cognitive processes and intelligence

Lower-order cognitive processes may be considered as a heterogeneous group of various cognitive functions. Thus, there is no unitary assessment approach. The evaluation of cognitive processes ranges from simple reaction times measure to the query of strategies adopted during problem solving tasks, and depends on the particular problem. For example, mirror tracing is a visual motor task to measure visual integration, hand-eye coordination and learning of new motor skills. During skill acquisition, subjects have to copy a figure, but with their hand being placed behind a barrier. Feedback from their copying performance is only visible in a mirror. Because a detailed description of cognitive assessments would go beyond the scope of this dissertation, the focus will exclusively be on the assessment of intelligence.

Intelligence can only indirectly be inferred. Basically, three main approaches can be distinguished: (1) Inference from an external criterion, (2) Psychometric testing (e.g., the classical intelligence test, resulting in intelligence quotient (IQ) scores), and (3) Inference from neurobiological correlates.

### 1.4.1 Inference from apparent behavior

Intelligence can be inferred from apparent behavior or linked to an external criterion. Usually, professional success is assumed to reflect the underlying intelligence. For instance, intelligence correlates positively with professional success, income or career advancement, and seems to be the single best predictor for the later position in society (Brody, 1992).

School marks are often used to determine criterion validity of intelligence test. For example IQ scores for $6^{th}$ graders in the U. S. correlate about .6 with years of subsequent training (Duncan, Featherman, & Duncan, 1972). According to a meta-analysis by Fraser and colleagues (1987), correlation coefficients between intelligence scores and school marks vary from .34 to .51, depending on the type of school and years of education. Thus, intelligence only moderately correlates (Cohen, 1992) with school performance, reflecting the fact that intelligence does not exactly mirror school performance, and limiting the significance of intelligence testing for prognostic use in the prediction of individual school careers. In fact, many aspects such as concrete learning opportunity, individual support and personality factors (e.g., achievement motivation), have an impact

on external criteria such as school marks, which may explain the moderate nature of correlations between intelligence scores and school marks.

### 1.4.2 Psychometric testing

Psychometric testing is the standard approach to infer about intelligence. Specific tasks, which are assumed to reflect individual differences in intellectual ability, are usually applied.

From the beginning of the 20th century on, the first scientific approaches were made to define, assess and evaluate intelligent behavior. An early and influential attempt has been introduced by Albert Binet, published as the Simon-Binet test in 1905 (Binet & Simon, 1905) and further refined by Lewis M. Terman as the Stanford-Binet test (Terman, Lyman, & Ordahl, 1915). Binet was asked by the French department of education to develop an assessment tool of children's intellectual capacity, aiming to detect and promote children with special needs. Binet designed a battery of items that were thought to reflect age-appropriate intellectual ability. Individual items ranked for chronological age (CA) allowed for inference about children's mental age (MA). Accordingly, the individual MA score for a given child was related to its CA, thus providing a mean to evaluate its general state of intellectual development. Originally, CA was distracted from MA, offering a crude possibility to infer about advance or delay of intellectual development. However, it was quickly realized that the MA-minus-CA-score did not reflect the extend of a developmental advance or delay. For example, it was not possible to distinguish between a four year old with a MA of two and a fourteen year old with a MA of twelve – in this case both would have a delay of two years. Therefore, in 1912 William Stern suggested a different method to relate MA and CA. He calculated the quotient of MA and CA and multiplied it by 100, hence creating the well-known intelligence quotient (IQ) score (Stern, 1912).

Although the Simon-Binet test is no longer used these days, two of Binets original methodological principles are still present in today's well-established IQ tests: (1) Adaptive testing, that is the principle to start with items assumed to match approximately the intellectual level of a given subject, with a subsequent gradual progression of item difficulty and (2) Relation of individual test scores to age-specific population norms which is based on the assumption that intellectual

ability just as many other human characteristics should be normally distributed in the general population.
IQ scores are calculated as follows:

IQ = (X-μ)/ ς * 15 + 100 (Individual test score (X) minus age-standardized population mean (μ), divided by the standard deviation (ς) of the age-standardized population and than multiplied by 15 and added to 100).

Most IQ tests use the IQ norm with a population mean of 100 and a standard deviation of 15. Alternatively, the standard norm with the population mean of 100 and a standard deviation of 10 is applied. Population norms are ideally calculated within narrowly defined groups (considering age and years of education) and based on a large number of subjects. Referencing an individual score to the population norm is the prerequisite for an interpretation of a given score and statistical inference. For example, a score of 108 is not significantly higher than a score of 102. Based on the assumption that IQ scores are normally distributed, roughly two thirds of the population should score within plus or minus one standard deviation of the mean (see e.g., Mackintosh, 1998). Those with scores lower than the mean minus one standard deviation (i.e., IQ < 85) are often labeled with "learning disability", although this definition is not ubiquitously accepted. Those with scores lower than the mean minus two standard deviation (i.e., IQ < 70) are often labeled as "mentally retarded" (DSM-IV, Sass, Wittchen, Zaudig, & Houben, 2003). Giftedness on the other hand is usually defined as scores higher than the mean plus two standard deviations (i.e., IQ > 130, Freeman, 1986).
Apart from the importance of relating a given score to the population norm, several other criteria should be met by IQ tests to achieve a minimum of quality factors: First, the test should be objective, i.e. the administers' influence on the subjects' performance should be negligible. Second, the test should be reliable, i.e. the result should be accurate and replicable. Reliability is usually determined as test-retest reliability, which relies on testing the same subject on separate occasions (either with identical or alternate forms of a given test) or on split-half reliability. Split-half reliability compares scores of odd items with scores of even items on a given test. Both, objectivity and reliability profit from standardization of the test instruction, the procedure, and the evaluation. Third, the test should

be valid, i.e. agree with some external, independent criterion. In the context of intelligence tests, validity is usually derived from correlations with educational (e.g., school marks) or occupational attainment (Mackintosh, 1998), despite the fact that these correlation coefficients are only of moderate magnitude (see page 28, Inference from apparent behavior).

Most of today's standard IQ tests are based on a psychometric definition of intelligence that features (a) A strong general factor for lower-order abilities and (b) A differentiation between fluid intelligence and crystallized intelligence (Hunt, 2005). Fluid intelligence, the non-verbal dimension of intellectual capacity which is the ability to solve new problems, independent of previously acquired knowledge was defined as "the influence of biological factors on intelligence" (Horn & Cattell, 1966). Crystallized intelligence on the other hand, is the ability to apply previously learned solutions to novel problems; it mainly relies on explicitly acquired knowledge.

In general, there are two types of IQ tests that are based on fundamentally different concepts - tests assuming a hierarchical structure of human abilities and tests assuming a general factor of intelligence. The hierarchical approach is empirically derived from factor analysis, with part of the variance in individual scores being assigned to a general and part of the variance being assigned to a unique factor. IQ tests within this conceptual framework consist of test batteries, requiring different kinds of cognitive processes. For example, the Wechsler Intelligence Scale for Children (WISC), based on David Wechsler's idea, who defined intelligence as "the global capacity of a person to act purposefully, to think rationally, and to deal effectively with his/her environment" (Wechsler, 1939, p.229), consists of a multidimensional hierarchical test battery. It comprises multiple different tasks and requires different cognitive abilities. In addition to the *full scale IQ*, the newest version of the WISC, the WISC-IV, comprises several indices, representing the major components of intelligence, namely *verbal intelligence*, *fluid intelligence*, *working memory* and *speed of processing*. All indices are sum scores of several sub-tests. It allows for a global statement of intelligence and additionally for an evaluation of the individual cognitive profile.

In contrast, there are psychometric tests which are based on the assumption of a general factor of intelligence (Spearman's "g-factor", Spearman, 1904, 1923). For example, the Raven's Progressive Matrices (RPM, Raven, 2003) consists of a

unitary task aiming to assess the general factor of non-verbal intelligence and inductive reasoning. The RPM consists of graphical matrices with a gradually increasing level of difficulty. For each matrix, a missing piece must be selected from a choice of similar matrices, which requires awareness of similarities and differences. Apart from the unitary nature of the RPM, this test is also assumed to be "culture-fair", which means that the results should not be influenced by the educational and cultural background of the testee (Mackintosh, 1998).

### 1.4.3 Neurobiological correlates

Intelligence can be inferred from neurobiological correlates. Early anthropometric approaches from the nineteenth century used total brain weight and volume as correlates of intelligence, assuming that bigger brains are better brains. Even though, there are in fact positive correlations between total brain volume and IQ scores, correlation coefficients are only small to moderate ($r \sim .3$, McDaniel, 2005), and there is no causal relation. Besides, many of these approaches were biased by sexual and racial aspects, frequently suiting scientifically justified racism (Gould, 1994). Summarizing studies that are based on voxel-based morphometry, Haier and Jung elaborated and upgraded the original idea of linking grey matter volume to intelligence. The *parieto-frontal integration theory* (P-FIT) implies that networks of grey matter volumes in specific brain areas (local aspects), but also interactions dependent on the connecting fiber tracts are the biological substrates of individual differences in intelligence (Jung & Haier, 2007).

A different approach, the so-called *mental-speed-approach* is based on the assumption that speed of processing in elementary cognitive tasks is related to psychometric intelligence. In general, reaction times (RTs) are slower with increasing load of information. However, subjects with higher IQ scores need less extra time to process additional information. In fact, the increase in RT with increasing load of information correlates about -.18 to -.23 with IQ scores (Jensen, 1987) which is considered rather low (Cohen, 1992). The strongest effects in this context seem to be for intra-individual variability of RTs, with higher IQ scores associated to lower variability of RT. Similar results have been obtained for the relation between visual or auditory inspection time and IQ scores, with negative correlations of about -.02 to -.41, indicating that time necessary for the comparison of two stimuli is shorter for those with higher IQ

scores (Deary, Caryl, Egan, & Wight, 1989). In sum, correlation coefficients of psychometric intelligence and mental speed are from close to zero to moderate (see Jensen, 1987; Vernon, 1983), with all associations between RTs and intelligence scores being negative. Thus, it may be concluded that "reaction times reflect basic cognitive operations which are involved in many forms of intelligent behavior" (Vernon, 1983). Surprisingly, despite the long tradition and large body of research on the mental speed approach, no single study examined this relationship in children.

Techniques such as positron emission tomography (PET), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI) have considerably contributed to a refinement of the mental-speed-approach. For example, profiting from the high temporal resolution that is offered by EEG-based methods, the relationship between brain physiology and psychometric intelligence could further be specified. In 2005, Thatcher and colleagues (2005) reported correlation coefficients of .6 between IQ scores and a combination of parameters derived from the waking EEG, such as phase delay, amplitude asymmetry, coherence, relative and absolute power and power ratios. Along the same lines, Klimesch and colleagues (1999) reported a double dissociation between resting (tonic) and event-related (phasic) α- and θ-power of the waking EEG: During quite wakefulness (eyes closed), a large α- but low θ-power is related to intelligence, whereas the opposite is true for event-related changes, with a large θ- but low α-power reflecting high intellectual ability. Variables derived from event-related potentials (ERPs) such as latency, amplitude, waveform and waveform variability of specific ERP components have also been related to psychometric intelligence. For example, the latency of the P300 component has been reported to negatively correlate with intelligence scores in healthy children (Martin, Delpont, Suisse, Richelme, & Dolisi, 1993), whereas the waveform of a specific ERP component (N1-P2 steepness of rise) was reported to positively correlate (r=.6) with intelligence scores (Caryl, 1994).

A seminal study, focusing on functional aspects of neural processing was performed by Richard Haier in 1988. Subjects engaged in a non-verbal IQ test were simultaneously scanned for their glucose metabolism rate (GMR). Surprisingly, those that reached the highest IQ scores displayed the lowest GMR. In other words: The higher the IQ score, the lower the cognitive effort or demand, which has become known as the *principle of neural efficiency* (Haier et

al., 1988.). Haier interpreted his finding as follows: …"intelligence is not a function of how hard, but rather of how efficient the brain works" (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992). Since then, many have replicated and further specified the neural efficiency effect. One of the limitations of Haiers' first experiment was the fact that he only investigated male subjects. Indeed, Neubauer and colleagues (2003) failed to confirm a similar negative relationship for female subjects. On a closer look, however, females displayed the neural efficiency effect too, but only for those tasks in which they performed superior than males (e.g., verbal tasks). The authors concluded from this finding that neural efficiency is modulated by a task-sex-interaction (Neubauer, Grabner, Fink, & Neuper, 2005). Apart from the influence of sex and the nature of task, several other factors seem to influence neural efficiency, for example the level of task complexity. Only a "moderate" level of task complexity seems to elicit the neural efficiency effect, whereas very complex tasks or very easy tasks failed to do so (Neubauer & Fink, 2003). The question remains, however, what exactly represents the "moderate" complexity level for a given subject and how to individually assess it.

In sum, over the last decades common lines emerged regarding the neurobiology of intelligence: First, general statements are formulated for specific abilities rather than global aptitude. Second, neurobiological correlates are related to the local, instead of the global anatomical level. Third, the focus is on dynamic rather than static aspects of processing. As a notion of caution, it has to be mentioned that neurobiological correlates are easily mistaken as a direct measurement of intelligence. There is, however, no causal relationship between physiological parameters and psychometrically assessed intelligence. Furthermore, there is no solid theoretical model linking physiological parameters of the central nervous system to intelligence as a behavioral trait and the reported magnitude of correlations between IQ scores and physiological parameters of the waking brain (e.g., waveforms of ERPs, cerebral metabolic rates) are only moderate ($r \sim .4$, Deary & Caryl, 1997).

### 1.5 Sleep: a trait and state-dependent perspective

Considering the relationship between sleep, cognition and intelligence, it is essential to differentiate clearly between the two fundamental concepts – traits and states. As mentioned earlier, intelligence is considered a *trait* whereas cognitive performances are *state*-dependent. The distinction between traits and state-dependence is, however, also important for sleep.

Many studies allude to the influence of experimental manipulations on the sleep pattern and sleep EEG at the state-level. For example, total or partial sleep deprivation and sleep fragmentation are known to result in changes of sleep latency, slow wave sleep (SWS) and the spectral composition of the sleep EEG (Akerstedt, Kecklund, Ingre, Lekander, & Axelsson, 2009; Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Van Dongen, Vitellaro, & Dinges, 2005). Beyond the effects of experimental manipulation on subsequent sleep, sleep restriction and deprivation may also impair cognitive processes such as working memory or executive functions (Durmer & Dinges, 2005; Ratcliff & Van Dongen, 2009).

However, the human sleep pattern also qualifies for a trait with characteristic individual sleep duration and chronotypes (Van Dongen, Vitellaro, & Dinges, 2005). It is likely that certain aspects of sleep architecture and regulation are also under genetic control (for recent overview see Andretic, Franken, & Tafti, 2008; Cirelli, 2005; Tafti, Maret, & Dauvilliers, 2005). Polysomnographic studies indicated that a significant proportion of the variance in NREM sleep stage 2, stage 4, slow wave sleep, and the density of rapid-eye-movements in REM sleep are in part genetically determined (Linkowski, Kerkhofs, Hauspie, Susanne, & Mendlewicz, 1989; Merica & Gaillard, 1985). Spectral analyses of the sleep EEG in twins revealed that the sleep EEG is among the most heritable traits in humans (Ambrosius et al., 2008; De Gennaro et al., 2008). For example, heritability for the amount of NREM sleep is estimated at about 50% (Linkowski, 1999). The trait-like stability of sleep stages is surpassed by individual profiles of sleep EEG power spectra (Buckelmüller, Landolt, Stassen, & Achermann, 2006; De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005). Furthermore, the intra-individual stability of power maps largely exceeded the effects that are evoked by experimental manipulations such as sleep deprivation (Finelli, Achermann, & Borbély, 2001). For instance, spindle frequency activity (SFA or sigma power, i.e.

spectral power in the 12- 15Hz range) is highly variable across, but highly stable within individuals (Scholle, Zwacka, & Scholle, 2007; Werth, Achermann, Dijk, & Borbély, 1997), thus representing a trait or phenotype of a given subject. Based on recent data of sleep EEG recordings in mono- versus dizygotic twins, a heritability estimate of 96% for NREM sleep power spectra for frequencies between 8 and 16Hz was found (De Gennaro et al., 2008). The spectral composition of NREM sleep EEG was suggested to be suitable for defining endophenotypes (Ambrosius et al., 2008). In summary, the human sleep EEG has consistently been described as a trait-like "fingerprint" characteristic, probably reflecting traits of the underlying brain anatomy (Finelli, Achermann, & Borbély, 2001).

However, despite converging evidence for sleep as a "fingerprint" in adults, there is only a single study pointing towards similar trait-like characteristics of children's sleep EEG, with a high *intra-individual* similarity, but high *inter-individual* variability of the sleep EEG power spectra for children aged eight- to twelve years old (see Empirical work, study III).

### 1.6 Sleep and cognitive processes – the state approach

Many studies have demonstrated that sleep can enhance performance of tasks learned during prior wakefulness. Evidence of sleep-dependent memory consolidation accumulated in humans and animals (e.g., Born, Rasch, & Gais, 2006; Maquet, 2001; Peigneux, Laureys, Delbeuck, & Maquet, 2001; Walker, 2009), applying a variety of paradigms for different types of learning.

In adults, several studies have highlighted the importance of specific sleep EEG variables and in particular sleep spindles or SFA for learning. For example, performance in a procedural learning task (Tamaki, Matsuoka, Nittono, & Hori, 2008), declarative memory retention after a night of sleep (Clemens, Fabo, & Halasz, 2005; Gais, Molle, Helms, & Born, 2002) and after a short nap (Schmidt et al., 2006), positively correlated with SFA. Moreover, by demonstrating locally increased SFA over areas that have been challenged by a motor learning task, it was shown that SFA does not only reflect learning improvement on a global, but also on a local level (Nishida & Walker, 2007). Sleep spindles, the hallmark of stage 2 NREM sleep involve short waxing and waning synchronous bursts of activity. Based on animal models, single cell recordings and anatomical studies of the spindle generating thalamocortical system, it was speculated that sleep spindles may play a dominant role in gating plastic changes during sleep and thus may be considered a candidate physiological mechanism for memory consolidation (Sejnowski & Destexhe, 2000; Steriade, McCormick, & Sejnowski, 1993).

However, there is also evidence for an important role of the slow waves in learning processes. In a visuo-motor learning task activating circumscribed right parietal cortical areas resulted in a local increase of SWA in NREM sleep during the subsequent night. Furthermore, this localized increase in SWA was shown to correlate with a performance increase after motor learning, suggesting that the increase in SWA reflects synaptic potentiation induced by learning (Huber, Ghilardi, Massimini, & Tononi, 2004). Similarly, locally decreased SWA was observed following synaptic depression which has been induced by immobilization of an arm (Huber et al., 2006). To directly test predictions from this study, subjects were explicitly deprived from sleep slow waves by acoustic stimulation after performing on the visuo-motor learning task and compared with subjects in a control condition. Those in the control condition improved over

night, whereas those that were deprived from sleep slow waves did not (Landsness et al., 2009). Likewise, performance in texture discrimination, a specific form of perceptual learning, has been impaired by SWA suppression (Aeschbach, Cutler, & Ronda, 2008). This was interpreted in light of the synaptic homeostasis hypothesis (Tononi & Cirelli, 2006) which states that plastic processes occurring during wakefulness result in a net increase in synaptic strength. Slow waves are then suggested as an opponent mechanism to downscale the synaptic strength to baseline levels, thus providing an efficient synaptic load in terms of space and energy and optimizing the signal- to noise ratio of synaptic transmission. Though this appealing hypothesis is supported by several lines of evidence, it is still a matter of debate whether the synaptic homeostasis hypothesis represents a general functional correlate of learning in the classical sense or whether it only applies to rather specific forms of learning, such as implicit learning.

Despite the vast amount of literature about the relationship between sleep and learning or cognitive processes in adults and animals (for a recent review see Walker, 2009), there are only little data in children. Basically two different approaches were taken to examine the sleep/cognition relationship in children: First, studies on the associations between sleep and cognitive processes in clinical populations and second, studies using experimental sleep manipulations to assess the associations between sleep and cognitive processes.

Several clinical populations are characterized by disturbed sleep patterns concordant with cognitive impairments. For example, sleep-related breathing disorders show negative effects on children's attention capacity and academic achievement (Blunden, Lushington, & Kennedy, 2001). Many studies in the clinical context lack, however, the clear distinction between state-effects of sleep on learning and trait-like associations between sleep and general intellectual ability. Furthermore, even though clinical studies consistently point towards a close relationship between sleep and a variety of cognitive processes such as learning, perceptual speed, working memory and executive functions, it remains unclear whether the relationship also holds for healthy children. In general, inference from clinical to normal populations has to be regarded with caution because the underlying structural and functional conditions may be fundamentally different between these groups and thus not comparable.

More direct insights into the associations between sleep and cognition are provided by studies which experimentally restrict sleep and determine cognitive processes. Randazzo and Muehlbach (1998) compared children restricted to sleep only 5 hours with a control group which was allowed to sleep 11 hours and found impaired cognitive processes (verbal creativity and cognitive flexibility) in the restricted group. Similarly, Sadeh and Gruber (2003) compared a control group over three consecutive nights with two groups of children whose sleep was either restricted or extended by one hour per night. Children with a sleep extension performed significantly better in a continuous performance test and a simple RT task than those with sleep restriction or no intervention. Comparing pre- to post-sleep performance without prior sleep restriction, several other studies argued for an important role of sleep for learning in children (e.g., Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008; Gomez, Bootzin, & Nadel, 2006). A recent review by Kopasz et al. (2009) summarizes studies about the impact of sleep on children's performance of working memory and memory consolidation. The authors highlight the importance of sleep for memory consolidation, and conclude that higher-order brain functions may be more susceptible to sleep deprivation than performance in simple memory tasks.

In sum, several lines of evidence point towards a close relationship between sleep and specific cognitive performance such as motor learning, working memory or memory consolidation. However, data is largely based on either clinical populations or adults. In children, little is known about the relationship between cognitive performance and sleep.

### 1.7 Sleep and intellectual ability – the trait approach

In adults, few studies have examined the relationship between sleep and intellectual ability. On the physiological level, the following variables of the sleep EEG have been included: distribution of sleep stages, percentage of NREM sleep, number of sleep cycles, and EEG power within specific frequency bands.

SFA or sleep spindles have been the main candidate in the search of a physiological variable for the relationship between sleep and intelligence on the trait-level. Total number of sleep spindles (Fogel, Nader, Cote, & Smith, 2007), the density of fast spindles at specific electrode sites (Bódizs et al., 2005), sigma power (Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2006; Schabus et al., 2008) and the percentage of total sleep time spent in stage 2 NREM (Bódizs et al., 2005) correlates with full scale IQ scores. Interestingly, reported effects are all positive in nature – the higher the SFA, the higher the IQ scores. Correlation coefficients between physiological variables of the sleep EEG and full scale IQ scores are of a moderate to substantial magnitude and vary between .44 (Schabus et al., 2006) and .76 (Fogel, Nader, Cote, & Smith, 2007), which is remarkably higher than those reported for the waking brain. It may be that high correlation coefficients for the sleeping brain trace back to the fact that interference with external cognitive or sensory stimulation during sleep is minimized. Thus, physiological variables assessed during sleep may be more reliable as correlates for psychometric intelligence than physiological measures during waking.

Based on the hypothesis that sleep spindles may represent a basis for synaptic potentiation leading to neural plasticity (Sejnowski & Destexhe, 2000; Steriade, McCormick, & Sejnowski, 1993), one could argue that sleep spindles do not only represent state-related short-term neurophysiologic changes induced by concrete learning experience, but may also reflect long-lasting structural and functional characteristics of the brain. In fact, sleep spindles are characterized by a trait-like component (Werth, Achermann, Dijk, & Borbély, 1997), and thus, may actually represent a neuronal substrate for intellectual ability, manifest on the trait-level.

In children, only a single study in a non-clinical population points towards the same direction: Busby and colleagues (1983) reported higher percentage of stage 2 NREM sleep in 10-year old boys with superior IQ scores compared to

those with average IQ scores, indirectly supporting the association between sleep spindles and intellectual ability.

In the clinical context, the pattern of the sleep EEG has been used to predict developmental outcome and later IQ scores in preterm infants (Beckwith & Parmelee, 1986) as well as in healthy children (Scher, Steppe, & Banks, 1996). For example, Becker and Thoman (1981) reported a positive relationship between the occurrence of intense rapid-eye-movements ("rapid-eye-movement storms") during REM sleep at the age of six month and later intellectual functioning at age one year. SFA and sleep spindles have also been associated with intellectual ability in developmentally delayed children (Bixler & Rhodes, 1968; Gibbs & Gibbs, 1962; Shibagaki & Kiyono, 1983), and it has been suggested that children with mental retardation exhibit either large amounts of SFA or virtually none (Bixler & Rhodes, 1968). In light of the earlier mentioned positive association between IQ scores and SFA in healthy subjects, increased SFA in children with mental retardation appears contra-intuitive on a first glance. However, Fogel and colleagues (2010) postulated that the relationship between intelligence and SFA may not be linear, but rather U-shaped or curvilinear, which would reconcile contradictory results in the field.

In contrast to clinical studies of children with neurological or genetic disorders, where the sleep EEG was used as physiological correlate of intellectual ability, research in healthy children has largely been based on behavioral parameters of sleep in association with intellectual or psychosocial outcome variables. Sleep duration, sleep quality, and daytime sleepiness have been suggested as potential modulators of children's daytime performance and intellectual ability. Several authors concluded that a minimal amount of sleep is necessary for adequate behavioral and cognitive functioning in children (Dahl, 1996; Nixon et al., 2008; Touchette et al., 2007). The assumption that sleep and in particular sufficiently long sleep duration is critically important for the developing brain is quite common. This was already prominently expressed in 1904 by G. Stanley Hall: "…no one should be allowed to go to school at all without (at least) nine hours of sleep…" (Hall, 1904). Intuitively, the dogma of "the longer the sleep duration, the better the intellectual performance" makes sense, but on the other hand, there are several popular science reports and anecdotes about gifted children which appear to require very little sleep (Grubar, 1985). Interestingly, earlier publications from the 1930s indeed reported negative correlations between sleep

duration and intellectual ability in children (Erwin, 1934; Reynolds & Mallay, 1933; White, 1931), which is corroborated by a cross-sectional study performed during this thesis (see Empirical work, study I). So far, the only systematic review on the influence of sleepiness, sleep duration and quality on children's daytime performance exclusively focused on school performance. Moreover, even though the reported effects in this meta-analysis (Dewald, Meijer, Oort, Kerkhof, & Bögels, 2009) were significant, they were rather small (ranging from r=0.069 for sleep duration to r=-0.133 for sleepiness).

Thus, the relationship between sleep duration, cognitive processes and intellectual ability may be more complex than common sense and intuitive beliefs imply. Furthermore, the assumed causality that sleep duration affects intellectual ability does not necessarily resist a critical analysis and may actually be misleading. In fact, a recent study in adolescents demonstrated that not sleep duration per se determined daytime executive functioning, but rather subjective sleepiness (Anderson, Storfer-Isser, Taylor, Rosen, & Redline, 2009). Moreover, inter-individual differences in sleepiness and neurobehavioral deficits due to sleep deprivation are characterized by a strong trait component (Van Dongen, Baynard, Maislin, & Dinges, 2004). Thus, the cognitive and neurobehavioral impairments after sleep deprivation may not exclusively be of a universal nature, but also be modulated by a strong individual component.

### 1.8 Summary on the background and rationale for this thesis

Despite the wide acceptance of a trait-like nature for both - sleep and intelligence - surprisingly little research is documented about the relationship between these two phenomena. While clinical evidence points towards an important role of sleep for state-dependent cognitive processes (i.e., specific learning tasks), the association between sleep and intelligence under non-pathological and non-experimental conditions (on the trait-level) is less established. Furthermore, most research within the field of sleep and intelligence has been performed in adults or students, whereas the natural, innate sleep behavior in healthy children in its relation with intellectual development has hardly been investigated at all. Moreover, it is unknown so far, whether sleep can be considered to be a trait in children.

During wakefulness, several functional and structural variables of the brain have been proposed as neurobiological correlates of intelligence. However, up to now, no comprehensive neurobiological model of intelligence has addressed developmental processes, such as maturation of the central nervous system - studies have either been performed in adults or specific clinical populations. In the context of the neural efficiency theory (see 1.4.3 Assessment of intelligence, Neurobiological correlates), several questions remain: Does neural efficiency represent a general principle or does it depend on maturational stages of the central nervous system? What are suitable parameters for the assessment of neural efficiency in children? Does neural efficiency only exist for the waking state or is it also reflected by night-time correlates during sleep?

In summary, this thesis addresses the following questions: Is there a relationship between sleep and intellectual ability in healthy children? If yes, which physiological or behavioral variables of sleep are related to which intellectual domain? What are the confounding variables influencing potential relationships between sleep and intellectual ability? Is the trait-like nature of sleep, reported for adults, also present in children? If there are associations between sleep and intellectual ability – what could be the neurobiological basis of such relations? Are these relations a global phenomenon or are there also local aspects of the relationship between sleep and intellectual ability?

# II Empirical work

Study I

## Association between sleep duration and intelligence scores in healthy children

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**ABSTRACT**

We examined the association between sleep behavior and cognitive functioning in 60 healthy children between 7 and 11 years of age under non-experimental conditions. Intellectual abilities were assessed by the Wechsler Intelligence Scale for Children (fourth edition) and sleep variables by questionnaires, actigraphy and sleep diaries. Correlation analysis revealed a negative association between sleep duration on weekends and measures of intelligence (*full scale IQ* ($r$=-.29), *fluid IQ* ($r$=-.36)). The regression coefficient for sleep duration on weekends was -6.11 (SE=2.09) indicating an increase of 6.11 points on *fluid IQ* scores for each hour of shorter sleep duration. Attention measures did not correlate with cognitive or sleep variables. Daytime sleepiness as a potential moderator of the relationship between sleep duration and cognitive performance was not related to cognitive or sleep variables.

We conclude that children with higher daytime cognitive efficiency (reflected by higher intelligence scores) show increased nighttime efficiency (reflected by shorter sleep duration). In the light of the *neural efficiency hypothesis*, the current results argue for an extension of the original theory – referring not only to daytime, but also nighttime behavior.

Keywords for indexing: sleep; intelligence; development; childhood

## INTRODUCTION

A number of theories have been proposed to explain the functions of sleep. For example, sleep plays a role for daytime behavioral performance (Banks & Dinges, 2007), is involved in metabolic processes of the brain (Benington & Heller, 1995) and the body (Tasali, Leproult, Ehrmann, & Van Cauter, 2008), may serve memory consolidation and learning (Walker, 2009) and facilitate brain plasticity (Tononi & Cirelli, 2006). Sleep has also been related to neuronal processes during brain development in early life. For example, Frank and colleagues showed that cortical plasticity in the visual system of developing kittens is strongly correlated with sleep time and intensity indicating that sleep may consolidate waking experiences during critical periods of development (Frank, Issa, & Stryker, 2001). In fact, sleep is the relevant behavioral state in the first years of life (Iglowstein, Jenni, Molinari, & Largo, 2003) emphasizing its importance related to neuromaturational changes occurring during childhood. However, the relationship between sleep and maturational processes may not only be on the structural and functional level of the central nervous system (Frank, Issa, & Stryker, 2001; Sowell et al., 2004), but also on the behavioral level. Along these lines, sleep may be important for developmental processes of cognitive functions and learning during childhood. This view of a close sleep/cognition relationship is supported by the observation that specific sleep characteristics are related to later developmental outcome (for review see Jenni & Dahl, 2008). In fact, the association between sleep and cognitive development in children has attracted increasing interest. Recent epidemiological surveys have highlighted negative consequences of chronic sleep deprivation on children's cognitive abilities (Nixon et al., 2008). Moreover, in clinical populations disturbed sleep patterns concordant with cognitive impairments have been described. For example, sleep-related breathing disorders show consistently negative effects on children's intellectual performance and academic achievement (Blunden, Lushington, & Kennedy, 2001). Psychiatric disorders such as attention deficits (Kirov et al., 2004) or major depression (Ivanenko, Barnes, Crabtree, & Gozal, 2004) are also known to adversely influence both sleep behavior and cognitive processes.

A more direct insight into the association between sleep and cognition is provided by studies which experimentally restrict sleep and assess cognitive performance. Randazzo and Muehlbach (1998) compared children restricted to sleep only 5

hours with a control group which was allowed to sleep 11 hours and found impaired cognitive functions (verbal creativity and Wisconsin Card Sorting) in the restricted group. Similarly Sadeh and Gruber (2003) compared a control group over three consecutive nights with two groups of children whose sleep was either restricted or extended by one hour per night. Children with a sleep extension performed significantly better in a continuous performance test and a simple reaction times task than those with sleep restriction or no intervention. Several other recent studies have also argued for an important role of sleep for learning and cognitive processes in children (Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008) by using experimental learning paradigms and comparing pre- to post-sleep performance levels or the wake condition. We note, however, that all of theses studies primarily focused on the learning aspect or state-level and do not allow conclusions about associations between sleep and cognition on the trait-level.

While clinical and experimental evidence points towards a role of sleep quality and quantity for cognitive functioning, the association between sleep and cognition in healthy children under non-experimental conditions is much less clear. Several authors have concluded that a minimal amount of sleep is necessary for adequate behavioral and cognitive functioning in children (Dahl, 1996; Touchette et al., 2007). Intuitively it makes sense that the longer the sleep duration, the better the cognitive performance. On the other hand, there are also popular science reports about gifted children which appear to require very little sleep (Grubar, 1985). Also earlier publications from the 1930s reported negative correlations between sleep duration and cognitive performance in children (Erwin, 1934; Reynolds & Mallay, 1933; White, 1931).

Overall, studies investigating the association between sleep and cognition have focused on clinical population or experimental manipulation, mostly without distinguishing between the state- and trait-level. Thus, the present study was performed to address the following two questions: (1) Is there a relationship between sleep and cognitive abilities in healthy children? (2) If so, which variables of sleep behavior are related to which cognitive dimension?

## METHODS

### Participants

A total of 63 healthy children (ages 7.5 to 11.2 years) were recruited from primary schools. Based on an initial screening interview, children with chronic diseases, neurological or psychiatric diagnosis (e.g., attention deficit hyperactivity disorder), sleep disorders or children under any medication (e.g., methylphenidate) were excluded. Because of incomplete data sets, three children were excluded which resulted in a total study population of 60 children, 34 boys and 26 girls (mean age= 9.4 years, standard deviation (SD) = 1.0). Socioeconomic status (SES) was determined according to Largo and Pfister (1989) on a scale combining paternal occupation and maternal education with a total score ranging from 2 to 12. In 51% of the families an upper range SES (10-12 points) was observed, while SES was in the middle range (6-9 points) in 47% of the families. Only one family (2%) belonged to the lowest SES group (2-5 points). In the *Strength and difficulties questionnaire* (Goodman, 1999), an often used symptoms checklist for behavioral and psychological problems, 90 % of the children were in the normal range on the total sum score, while 5% scored borderline and another 5% abnormal which is comparable to other epidemiological surveys (Woerner et al., 2002). Pubertal development status was assessed with a translated rating scale for pubertal development (Carskadon & Acebo, 1993) filled out by the parents. Ninety-one percent of our study population were prepubertal, 7% early pubertal and 2% (one child) mid-pubertal. The amount of television watched was assessed by asking parents about their children's habits. Thirteen percent of our population did not watch TV at all or only very rarely, 52% watched for one to five hours per week, 30% watched for five to ten hour per week and only 5% watched for ten hours or more per week. Children did not perform any kind of intelligence test for at least the last two years prior to participation in the present study.

### Measures

#### Cognitive and attentional variables

All children were assessed with the German version of the *Wechsler Intelligence Scale for Children (WISC IV,* Petermann & Petermann, 2007) yielding separate indices for *fluid intelligence*, *verbal intelligence*, *speed of processing* and *working memory* as well as a full scale *intelligence quotient* (*IQ)* score. WISC IV scores

are standard scores based on age-referenced normative data with a population mean of 100 and a standard deviation (SD) of 15. A children's test battery for the assessment of attention (*KITAP*, Zimmermann & Fimm, 1993) was also administered to assess different parameters of attention. The *alertness* subtest of the KITAP provided median and SD of reaction times based on age-referenced normative data. A combined score reflecting median reaction time and SD was calculated and referred to as *alertness* with a population mean of 50 and a SD of 10. The *go/nogo* subtest of KITAP also provided mean reaction time with a population mean of 50 and a SD of 10.

**Sleep behavior variables**

Questionnaire data: Parents filled out the *Children's ChronoType Questionnaire (CCTQ,* Werner, Lebourgeois, Geiger, & Jenni, 2009) which assesses sleep behavior variables such as bed times, lights off, sleep latency, wake up time, napping and get up time separately for weekdays and weekends. According to the parents, none of the children took regular naps, neither on weekdays nor on weekends. Furthermore, children's chronotype was determined by asking the parents whether their child is (1) definitely a morning type, (2) rather a morning type, (3) neither nor, (4) rather an evening type, (5) definitely an evening type or (6) unratable. The measures derived from the CCTQ included: (a) *Sleep period*, defined as sleep start (sleep latency added to the time of lights off) to sleep end (wake up time), (b) *Mid-sleep point on weekends*, defined as half of the sleep duration added to the sleep start. Sleep period was calculated separately for weekdays and weekends. For get-up time on weekends, parents were explicitly asked whether the child wakes up on his or her own or is awakened by a family member or by an alarm-clock. Except for one child with missing data, all children woke up on their own. Thus, week-ends seemed to be free of social constraints regarding wake-up times. Daytime sleepiness was assessed by the *Pediatric Daytime Sleepiness Score (PDSS,* Drake et al., 2003), a sum score combining eight different daytime sleepiness items on a 5-point scale (parent report).

Actigraphy and sleep diary: Following the cognitive assessment, all children were monitored at home for seven to fourteen consecutive days with an actigraph (AW4, Actiwatch Plus®, Cambridge Neurotechnology, Cambridge, UK) which is an activity-based wristwatch-like monitor that records physical activity based on

omni directional acceleration. Data were recorded in one-minute epochs (Activity and Sleep Analysis 5®). Actigraphy data were analysed with medium sensitivity by a scoring algorithm defined by Acebo (2005)and further described in detail by Werner et al. (2008). Ninety percent of the children wore Actigraphs for thirteen days or more, with a minimum of two weekend days and five weekdays. During the Actigraph monitoring, parents were requested to keep a sleep dairy recording bed time, lights off and get-up time, as well as reports about child's state of health and periods where the Actigraph was not worn. Most children wore actigraphs continuously across 24 hours, but some had difficulties wearing actigraphs due to sports activities. Since none of the children had daytime naps, we asked them to wear the device at least from 6 p.m. to midday. Parents were explicitly asked about their child's health for every day of actigraphy recording with given categories of (1) child is healthy, (2) feels a little sick and (3) is definitely sick. Days with missing diary information or references to sickness (category 2 and 3) were discarded from the analysis. The following actigraphic sleep variables were included for the analysis: (a) *Assumed sleep time*, defined as the difference between sleep start time and sleep end time and (b) *Mid-sleep point*, defined as half of the sleep duration added to the sleep start. *Assumed sleep time* as well as *mid-sleep point* were calculated separately for weekdays and weekends.

**Procedure**

The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki. Children were recruited sequentially from October 2007 to October 2008 across all seasons. All families received a detailed study description and provided written informed consent. After oral information about purpose and procedure of the study, children were assessed by a trained psychologist with the German version of the *WISC IV* intelligence test (Petermann & Petermann, 2007). They then performed the two subtests *alertness* and *go/nogo* of the *KITAP* (Zimmermann & Fimm, 1993). At the same time, parents filled out questionnaires about their children's sleep behavior (*CCTQ* and *PDSS*) and about their biographical background. After the session, the Actigraph was adjusted to the child's wrist and the sleep diary was explained to parents. Finally, the children were rewarded for their participation with gift

vouchers worth 30 CHF. Actigraphs were sent back by surface mail after 14 days of recording.

Actigraphy recording for 14 days occurred during school time only, but not during vacation times, usually right after the assessment session.

**RESULTS**

Descriptive data of cognitive variables and sleep behavior are presented as mean ± SD in Table 1-1 and 1-2. Scores of full scale *IQ* and all individual indices were above average ($p<.05$, one-sample t test), but with normal SD (see discussion). Sleep behavior was in the normal range and consistent with another study using a similar study population (Iglowstein, Jenni, Molinari, & Largo, 2003). All but the two sleep variables *sleep period on weekdays (questionnaire)* ($p<.05$) and *daytime sleepiness (assessed as sum score of the PDSS)* ($p<.01$) showed normal distribution (Kolmogorov-Smirnov test). The mean score of the PDSS was 8.1 (SD = 3.9). While none of the measures of sleep behavior differed between girls and boys, two of the cognitive variables differed (independent-samples t tests): Girls obtained better scores on the *speed of processing* index ($t\ (58) = -3.4,\ p<.001$) and had higher scores of *alertness* ($t\ (58) = -2.2,\ p<.05$). Children characterized by parent report as definitively an evening type showed later *mid-sleep point on weekends* than morning types (analysis of variance, $F\ (4,55) = 5.05$, $p<.01$). However, chronotype was not related to any of the cognitive performance variables or attentional parameters.

In an explorative analysis, partial correlations controlling for *age* and *SES* were computed among cognitive and sleep behavior variables (Table 1-3). Overall, the highest correlation coefficients were observed between the sleep behavior *sleep period on weekends (questionnaire)* and *full scale IQ* ($r=-.29$, $p<.05$), *fluid IQ* ($r=-.36$, $p<.01$) and *working memory* ($r=-.27$, $p<.05$). All correlations were negative: the shorter the sleep duration, the higher the score of the cognitive variables. The association between *assumed sleep time on weekends (assessed by actigraphy)* and cognitive variables were pointing towards the same direction, but were weaker. Consequently, only sleep duration assessed as *sleep period on weekends (questionnaire)* was used for further analysis (see discussion). Correlations between sleep duration derived from actigraphy versus questionnaire were r=. 638 (p<.001, weekend only) and r=.598 (p<.001, weekdays only).

Table 1-1: Descriptive data of cognitive variables assessed by HAWIK IV and KITAP (n=60)

| | mean (M) | standard deviation (SD) | range |
|---|---|---|---|
| IQ | 112.2 | 12.6 | 85 - 141 |
| Fluid IQ | 113 | 13.5 | 88 - 143 |
| Verbal IQ | 111.9 | 13.4 | 90 - 144 |
| Speed of processing | 110.1 | 12.6 | 76 - 136 |
| Working memory | 104.1 | 12.9 | 77 - 141 |
| Alertness | 55.2 | 7.7 | 40 - 74 |
| Reaction time Go/Nogo | 56.1 | 10.1 | 28 - 78 |

Population norms for full scale IQ and indices fluid IQ, verbal IQ, speed of processing and working memory are M=100 and SD=15.
Population norms for alertness and go/nogo are M=50, SD=10.

Multiple linear regressions were performed for predicting scores of the different cognitive variables. The predictors were *age*, *SES* and *sleep period on weekends (questionnaire)*, while full scale *IQ* and the individual indices *fluid IQ,* and *working memory* were used as criterion variables.
The full scale *IQ* could not be predicted by *age*, *SES* and *sleep period on weekends (questionnaire)* ($R^2$ =.10, adjusted $R^2$ =.05, $F$ (3, 56) = 2.07, $p$=.12). Similarly, *working memory* could not be predicted by *age*, *SES* and *sleep period on weekends (questionnaire)* ($R^2$ =.11, adjusted $R^2$ =.06, $F$ (3, 56) = 2.34, $p$=.08). The statistic model did not reach significance for the prediction of full scale IQ and working memory. Following statistical conventions, the individual coefficients (though reaching significance) are not reported.
In contrast, *fluid IQ* was predicted by s*leep period on weekends (questionnaire)* ($R^2$ =.14, adjusted $R^2$ =.09, $F$ (3, 56) = 2.96, $p$<.05), with shorter sleep period on weekends associated with higher scores of *fluid IQ* ($r$=.-.36, $p$=.05, partial correlations controlled for *age* and *SES*). *Sleep period on weekends (questionnaire)* alone accounted for approximately 13 % of the variance. The non-standardized coefficient for *sleep period on weekends (questionnaire)* was -6.11 (standard error=2.09, $p$<.01) indicating an increase of 6.11 points on the

score of *fluid IQ* for each hour of shorter sleep duration. The coefficients for *age* and *SES* were not significant.

Table 1-2: Descriptive data of sleep behavior derived from questionnaires and actigraphy (n=60)

| | mean | standard deviation | range |
|---|---|---|---|
| Assumed sleep time (weekends only; hours.minutes) Actigraphy | 09.34 | 00.30 | 08.05 – 11.04 |
| Assumed sleep time (week days only; hours.minutes) Actigraphy | 09.26 | 00.29 | 08.14 – 10.10 |
| Sleep period (weekends only; hours.minutes) Questionnaire | 10.08 | 00.49 | 08.18 – 12.10 |
| Sleep period (week days only; hours.minutes) Questionnaire | 09.45 | 00.32 | 07.50 – 10.40 |
| Mid sleep point (weekends; time of day) Questionnaire | 02:59 h | 00.41 | 01:10 – 04:40 h |
| Mid sleep point (weekends; time of day) Actigraphy | 02:21 h | 00.43 | 00:43 – 04:06 h |

Table 1-3: Partial Correlations (controlled for age and SES) between cognitive variables and sleep behavior (n=60)

| | Assumed sleep time (weekend) Actigraphy | Assumed sleep time (week days) Actigraphy | Sleep period (weekend) Questionnaire | Sleep period (week days) Questionnaire |
|---|---|---|---|---|
| IQ | -.24 # | -.15 | **-.29 *** | -.24 # |
| Fluid IQ | **-.30 *** | -.13 | **-.36 **** | -.16 |
| Verbal IQ | -.23 # | -.16 | -.14 | -.23 # |
| Speed of processing | .06 | .01 | -.08 | -.12 |
| Working memory | **-.29 *** | -.21 | **-.27 *** | -.24 # |

# p<.1, * p<.05, ** p<.01; significant values in bold

**DISCUSSION**

In a multimethod approach the present study consistently showed a negative association between *sleep duration on weekends (questionnaire)* and IQ scores on several dimensions in healthy children between 8 to 11 years of age. Thus, the shorter the habitual sleep duration on days that were not influenced by social constraints, the higher the scores of cognitive performance – *full scale IQ, fluid IQ* and *working memory*. These findings confirm previous reports of the early 1930s (Erwin, 1934; Reynolds & Mallay, 1933; White, 1931) and are in line with recent data of the Zurich Longitudinal Studies which also showed a negative relationship of similar magnitude between cognitive abilities and sleep duration ($r$=-.3 to -.4) in children and adolescents between 7 and 16 years of age (Jenni, Caflisch, & Molinari, 2009).

Sleep duration variables which were objectively assessed by actigraphy over 14 days pointed in the same direction – a negative correlation between sleep duration and cognitive abilities - but the correlations were in general weaker than those between cognitive measures and sleep duration variables assessed by questionnaire. We decided to use the questionnaire data instead of the

objectively assessed actigraphic parameters for the regression analyses, based on the assumption that sleep duration assessed by questionnaire may more adequately reflect children's habitual sleep behavior. In fact, habitual sleep behavior may be better characterized by parent report providing a more global measure of sleep duration compared to the snapshot-like recording of sleep behavior over 14 days which may be influenced by physical health, weekly activities, temporary fluctuations and biases. Actigraphic recording over a prolonged time period (several weeks) would be needed to assess habitual sleep behavior which was not possible.

The children were healthy, did not complain about sleep disorders or behavioral problems, obtained daytime sleepiness scores on the PDSS that were comparable to other studies using this sleepiness measure (Perez-Chada et al., 2007) and were scoring in the normal range of attention measures. We also note that the negative association between sleep duration and cognitive abilities was not dependent on children's chronotype. Thus, the possibility that the effect is primarily caused by the children's preference for certain times of the day (i.e., evening preference) which may interfere with social demands is not supported. Cognitive abilities were in general above average, which is probably resulting from the voluntary study participation and the specific population that is eager to participate in these psychological studies, thus limiting the generalization of the current results. Since SD and range of cognitive variables reflected a normal population range, however, we are confident that the results of the present study are not purely attributable to the specific population.

For the interpretation of the negative association between sleep duration and cognitive performance - which seems to be contrary to what is generally assumed - two plausible explanations may be offered: First, it may be argued that children with a short sleep duration benefit from a long wake-time. The waking state offers constant opportunities for cognitive stimulation, social interactions and multisensory input which are all crucial for children's development. Because sleep duration shows large interindividual variability as well as intraindividual stability (Jenni, Molinari, Caflisch, & Largo, 2007), we may assume that children characterized by short sleep durations were more stimulated over the years compared to those with longer sleep duration. Finally, it may be speculated that those with shorter habitual sleep duration may benefit

from this extra wake-time in terms of higher scores on intellectual ability measures.

An alternative explanation may be based on the *neural efficiency theory* (Haier et al., 1988). Based on a negative correlation between cortical glucose metabolism rate and scores on fluid intelligence they concluded that "intelligence is not a function of how hard, but rather of how efficient the brain works" (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992 ,pp. 415-416). In this framework, psychometrically assessed IQ scores have been associated to several physiological variables such as glucose metabolism rate and an electroencephalographic measure, the event-related desynchronization (Neubauer & Fink, 2009). Overall, theses studies have consistently revealed a negative relationship between IQ scores and physiological variables; in other words, higher IQ scores were related with lower cortical activation. According to this theory, *neural efficiency* may represent a phenomenon that relates a psychological trait (e.g., intelligence) to a physiological mechanism (e.g., neuronal processing). In the view that children spend a considerable time of the 24-h period asleep, our results may argue for an extension of the original theory – referring not only to daytime, but also to nighttime behavior. Children with higher cognitive efficiency, reflected by higher scores of cognitive measures, may also display higher nighttime efficiency (i.e. more efficient neuronal recovery) reflected by shorter sleep duration. Along these lines, a negative relationship between sleep duration and cognitive measures would complete the picture of the *neural efficiency theory*. After all, sleep as well as cognition are both related to neuronal processing and thus should have some common properties. Notably, this hypothesis needs to be further corroborated including physiological measures of sleep derived from polysomnographic recordings. In fact, two recent studies in young adults have shown high correlations ($r > 0.75$) of sleep spindle activity during night sleep and intellectual abilities (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007).

Interestingly, the highest correlation was found between *sleep duration on weekends (questionnaire)* and *fluid IQ* ($r=-.36$, $p<.01$). *Fluid IQ*, the non-verbal dimension of intellectual capacity (e.g., the ability to solve new problems, independent of acquired knowledge) was defined as "the influence of biological factors on intelligence" (Horn & Cattell, 1966). Based on Horn and Cattell's concept, *fluid IQ* may be understood as the component of intellectual ability

which is more closely related to neuronal processing of the brain; in other words, *fluid IQ* may reflect the "hard-ware" of human intelligence. At this point, the line of arguments emerging from the present data converges with earlier studies which identified neuronal correlates of intelligence. They reported that the association between neuronal correlates and cognitive performance is higher for the *fluid IQ* than the full scale IQ or other dimensions of cognitive performance (Thatcher, North, & Biver, 2005).

Several studies have shown that sleep loss is associated with cognitive impairment, developmental disorders and behavioral problems in children and adolescents (Dahl, 1996; Nixon et al., 2008; Sadeh, Gruber, & Raviv, 2003; Touchette et al., 2007). These findings have led to the assumption that sleep is critically important for children's development and, thus, short sleep should be avoided. The latter was already prominently expressed in 1904 by G. Stanley Hall ("…no one should be allowed to go to school at all without (at least) nine hours of sleep…" (Hall, 1904)). Notably, the current findings indicate that the issue is far more complex. Taking individual differences or the trait-level into account, a negative relationship between habitual sleep duration and intelligence scores was found which seems counter-intuitive. Given that children are healthy and not sleep restricted, however, it may well be presumed that their individual sleep need meets what is necessary for adequate cognitive functioning. We would like to stress that our results are only of a correlational nature and, thus, have to be interpreted with caution. Therefore, it is not recommended to restrict sleep of children in order to improve cognitive outcome, rather the opposite - a deterioration of cognitive performance - will occur as shown previously (Randazzo, Muehlbach, Schweitzer, & Walsh, 1998; Sadeh, Gruber, & Raviv, 2003). We call for accepting the individual sleep need of children and matching sleep schedules according to their needs (Jenni & O'Connor, 2005).

**Addendum: Intellectual ability, sleep duration and "social jetlag"**

It has repeatedly been reported that adults and adolescents sleep significantly longer on free days than on scheduled days during the week, which has been interpreted as an accumulated "sleep deficit" (Carskadon, Vieira, & Acebo, 1993; Roenneberg et al., 2004; Wolfson & Carskadon, 1998). The accumulated sleep deficit has also been associated to more struggles at school in adolescents (Wolfson & Carskadon, 1998). Besides, not only the accumulated sleep deficit, but also the interaction or discrepancy between the biological clock (endogenous component) and the societal clock (environmental demands) has recently gained attention, possibly causing a chronic form of jetlag, the so-called "social jetlag" (Wittmann, Dinich, Merrow, & Roenneberg, 2006).
The Kindergarten-children aged four to seven years old, included in study II, already accumulated a sleep deficit during the week – they slept 18 minutes longer on free days than on scheduled days during the week. They also shifted their mid-sleep point approximately 34 min from week days to free days (for details see Werner, Lebourgeois, Geiger, & Jenni, 2009).

We hypothesized that school-age children too may accumulate a sleep deficit during the week and sleep longer on free days (holidays and weekends) than on scheduled days during the week. Consequently, we further expected a relationship between accumulated sleep deficit and intellectual ability, in the sense that those children with higher sleep deficit (longer sleep durations on free days) may have more difficulties during the week to sustain adequate levels of alertness for cognitive performance.
Besides, we also hypothesized that those children with a larger delay of sleep phase between week days and free days (more socially jet-lagged) would be more affected by daytime sleepiness which in turns may even affect their daytime cognitive performance.

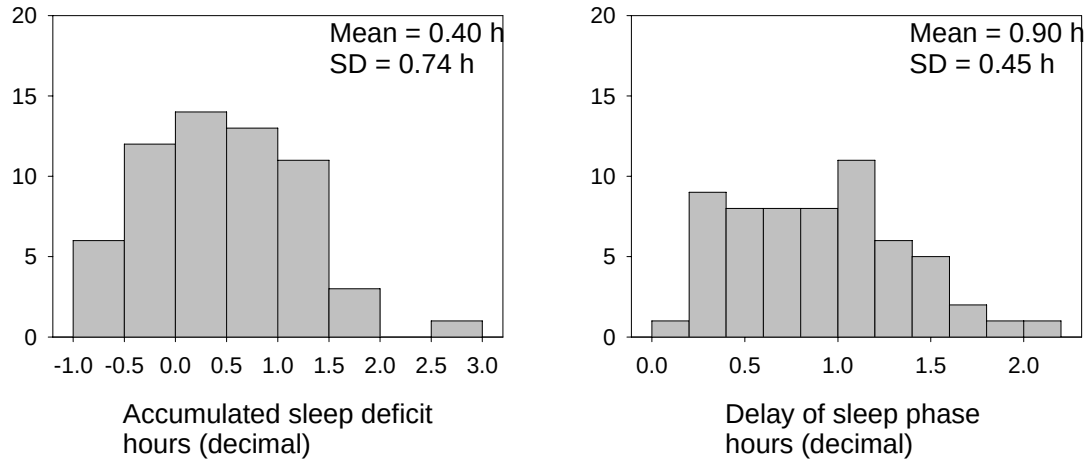
In our study population of 60 healthy children (34 male), aged 7.5 to 11.2 years old (mean age=9.4 years, SD=1.0), the mean difference in sleep duration between week days and free days (assessed by questionnaires) was approximately 24 minutes (SD=44 min). Thus, school-age prepubertal children

accumulate a sleep deficit during the week of almost half an hour. However, approximately one fourth of our study population slept even less on free days than on scheduled days during the week (see fig. 1-1). Probably, those with shorter sleep durations on free days compared to week days do not need as much sleep as assumed and imposed by their parents. When free to choose their sleep duration by their own (i.e., on free days), they prefer to sleep less than during the week.

Besides, it is important to note that sleep duration is only a single (behavioral) indicator, assumed to reflect the underlying sleep pressure or homeostatic drive. In fact, sleep intensity, as derived from SWA appears to be a more important and direct physiological indicator of sleep homeostasis. After total or partial sleep deprivation, sleep intensity, reflected by SWA is increased in the subsequent recovery night to a much larger extend compared to the sleep duration (see "two process model of sleep regulation" Borbély, 1982; Daan, Beersma, & Borbély, 1984). Therefore, the conclusion that those children who sleep less during the week are chronically sleep deprived may not necessarily be valid. It may just as well be the case that the slightly shorter sleep duration during the week is compensated by higher sleep intensity (i.e., more SWA). Since we did not assess SWA as a physiological marker of sleep pressure or homeostatic drive, it is not possible to draw any conclusions about the consequences of the discrepancy between sleep duration on scheduled versus non-scheduled days.

The mid-sleep point on free days was 54 min (SD=27 min) later than the mid-sleep point on week-days (mid-sleep point for week days: 2:04 a.m., mid-sleep point for free days at 2:58 a.m.). Thus, school-age prepubertal children delay the timing of their sleep during free days for approximately one hour. It is known that the mid-sleep point on free days (MSF) is shifted towards later hours during puberty (Carskadon, Vieira, & Acebo, 1993; Roenneberg et al., 2004). However, the children of our study population were mainly prepubertal (54 out of 60). The later mid-sleep point on free days compared to week days suggests that children are rather free to chose the timing of their sleep on free days than on days during the week. Since we did not collect plasma melatonin or other physiological circadian markers, we cannot draw any conclusions about the reason for this phase delay (i.e., endogenous or exogenous).

Figure 1-1: Distribution (number of children) of children's accumulated "sleep deficit" (difference between sleep duration on free days and sleep duration during the week) and delay of sleep phase (difference between mid-sleep point on free days and mid-sleep point on week days). N=60




In an exploratory analysis partial correlations (controlled for age and SES) between cognitive variables *(full scale IQ, verbal IQ, fluid IQ, working memory, speed of processing*) and *accumulated sleep deficit* (determined as the sleep duration on free days minus the sleep duration on scheduled days during the week) were calculated. Fluid IQ was significantly related to accumulated sleep deficit ($r$=-.30, $p$<.05). Thus, children with a larger accumulated sleep deficit had lower scores in the fluid IQ index. None of the other cognitive variables was related to accumulated sleep deficit.

Partial correlations (controlled for age and SES) were then calculated between cognitive variables *(full scale IQ, verbal IQ, fluid IQ, working memory, speed of processing*) and *delay of sleep phase* (determined as the mid-sleep point on free days minus the mid-sleep point on week days). None of the cognitive variables was related to delay of sleep phase.

Finally, the relationship between the different behavioral variables of sleep was explored, calculating partial correlations (controlled for age) between *accumulated sleep deficit*, *delay of sleep phase*, *morningness/eveningness (M/E)*

*score* (reflecting the children's chronotype, see study II for details) and the *PDSS score* (reflecting daytime sleepiness). There were significant correlations between all four behavioral sleep variables (*accumulated sleep deficit*, *delay of sleep phase*, *M/E score*, *PDSS)* (see table 1-4).

Table 1-4: Partial correlations (controlled for age) between different behavioral sleep variables (N=60).

| | Delay of sleep phase | M/E score | PDSS |
|---|---|---|---|
| Accumulated "sleep deficit" | .44 ** | .32 * | .32 * |
| Delay of sleep phase | | .38 ** | .32 * |
| M/E score | | | .71 *** |

* p<.05, ** p<.01, *** p<.001

Children with a higher accumulated sleep deficit (difference between sleep duration on free days and sleep duration during the week), were also characterized by a larger delay of sleep phase (difference between mid-sleep point on free days and mid-sleep point on week days), higher scores of the M/E score (rather "evening types") and higher scores of daytime sleepiness.

In sum, we can rule out the possibility that the negative association between sleep duration and intellectual ability reported in study I is related to children's chronic sleep deprivation. Although, there is a significant correlation between accumulated sleep deficit and fluid IQ (lower fluid IQ scores in those children characterized by a larger sleep deficit), this effect does not adequately explain the consistent results reported in study I. The association between sleep duration and cognitive variables was consistently a negative one (present on week days as well as on weekend days), although not significant for the week days (see study I, table 1-3 in the manuscript "Associations between sleep duration and intelligence scores in healthy children").

Study II

# Assessment of chronotype in four-to eleven-year-old children: Reliability and validity of the Children's ChronoType Questionnaire (CCTQ)

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**ABSTRACT**

Individual differences in circadian phase preference ("chronotype") are linked to sleep schedule variability, psychosocial functioning, and specific properties of the circadian clock. While much is known about the development, distribution, and variability of chronotype in adolescents and adults, assessment in prepubertal children has been hindered by lack of appropriate, reliable and valid measures. This study presents a detailed description of the assessment of children's chronotype by the Children's ChronoType Questionnaire (CCTQ). The CCTQ is a parent-report 27-item mixed-format questionnaire resulting in multiple measures of chronotype in 4- to 11-year-old children: the mid sleep point on free days (MSF), a morningness/eveningness scale (M/E) score, and a 5-point Chronotype (CT) score. The study provides validity data using actigraphy, as well as test-retest reliability data for all three chronotype measures and sleep/wake parameters. Overall, the findings indicate moderate to strong agreement between the three measures, adequate associations between chronotype measures and sleep/wake parameters assessed by actigraphy, and excellent temporal stability (reliability).

Keywords: chronotype, mid sleep point, morningness/eveningness, validity, children

Abbreviations:
SC – Scheduled Days
FR – Free Days
MSF – Mid Sleep point on Free days
M/E – Morningness/Eveningness
CT – ChronoType
SD – Standard Deviation
MEQ – Morningness-Eveningness Questionnaire
CSM – Composite Scale for Morningness

## INTRODUCTION

Chronotype is an individual difference characteristic reflecting the time of day at which individuals are "at their best" (Guthrie, Ash, & Bendapudi, 1995; Kerkhof, 1985). While some people prefer to wake up early in the morning and are most alert in the first part of the day, others' peak time of day is during the evening hours and prefer to go to bed late at night (Cofer et al., 1999; Tankova, Adan, & Buela-Casal, 1994). Studies in adults and adolescents show that morning-types (also called "larks") have an earlier sleep schedule [e. g., (Carskadon, Vieira, & Acebo, 1993; Horne & Ostberg, 1976; Kerkhof & Lancel, 1991; Mecacci & Zani, 1983)], an earlier circadian temperature phase [e.g., (Bailey & Heitkemper, 2001; Duffy, Dijk, Hall, & Czeisler, 1999; Kerkhof, 1991; Kerkhof & VanDongen, 1996; Mongrain, Lavoie, Selmaoui, Paquet, & Dumont, 2004)], an earlier melatonin secretion pattern (Laberge et al., 2000), and report fewer difficulties with sleepiness and attention (Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002) than evening-types ("owls"). Thus, individual differences in chronotype are linked to sleep schedule variability, psychosocial functioning, and specific properties of the circadian clock.

Chronotype is also referred to as 'morningness/eveningness' (M/E) preference, which reflects an individual's standing on a continuum between two extremes (Natale & Cicogna, 2002). Chronotype is assessed through self-report questionnaires. In adults, Horne and Östberg's Morningness-Eveningness Questionnaire (MEQ, Horne, 1976) estimates M/E preference by asking respondents about their preferred timing of sleep and daily activities. The MEQ has been validated across a variety of samples [e.g., (Chelminski, Ferraro, Petros, & Plaud, 1997; Posey & Ford, 1981; Taillard, Philip, Chastang, & Bioulac, 2004)], translated into several languages [e.g., (Mecacci & Zani, 1983)], and revised into other versions [e.g., Smith's Composite Scale of Morningness (CSM ,Smith, Reilly, & Midkiff, 1989); Adan and Almirall's rMEQ (Adan & Almirall, 1991)]. To evaluate M/E preference in adolescents, Carskadon and colleagues (1993) modified adult measures of chronotype (Horne & Ostberg, 1976; Smith, Reilly, & Midkiff, 1989) into an adolescent-friendly self-report of daily preference. In contrast to these multi-item measures, Roenneberg and colleagues (Roenneberg, Wirz-Justice, & Merrow, 2003) developed the Munich ChronoType Questionnaire (MCTQ), which estimates individual's circadian preference by a single phase-reference point, the mid-sleep point on free days (MSF). The self-

report MCTQ has been used in adults, adolescents, and children as young as 10 years of age (Roenneberg , Date accessed: 12.11.08). The MCTQ's validity in adults and adolescents is evidenced by strong concordance with MEQ scores [MSF: r=-.73 (Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005)] and with CSM scores [MSF: r=-.62 (Randler, 2008b)]. Reliability and validity data for MSF in children, however, have not been reported. Furthermore, a parent-reported version for assessment of chronotype in prepubertal children is not currently available.

The assessment of individual chronotype is important not only for the diagnosis and treatment of circadian sleep disorders (Baehr, Revelle, & Eastman, 2000) and for predicting the ability to adapt to specific work schedules (Costa, Lievore, Casaletti, Gaffuri, & Folkard, 1989; Costa, Sartori, & Akerstedt, 2006; Pisarski et al., 2006), but also for improving individual's daytime performance by matching sleep schedules to circadian biology (Silva, 2008). In particular, extreme evening types are at higher risk than morning types of not obtaining sufficient sleep and performing poorly due to discordance between their individual circadian rhythm and social demands [e.g., work and school schedules (Takeuchi et al., 2001; Wittmann, Dinich, Merrow, & Roenneberg, 2006)]. Evidence is also accumulating that subjects have more difficulties in maintaining sleep when sleep is scheduled at adverse circadian phases (Silva, 2008).

Overall, little is known about the development, distribution, and variability of chronotype in prepubertal children. Childhood sleep problems, such as bedtime resistance, sleep onset delay, prolonged nightwakings, and difficulties waking in the morning, are common parental complaints, affecting approximately 25% of children during the first 10 years of life (Jenni, Fuhrer, Iglowstein, Molinari, & Largo, 2005; J. Owens, 2007). Some have argued that behavioral sleep problems during childhood may occur because individual sleep and circadian characteristics are not matched with parental expectations or family and school schedules (Jenni & O'Connor, 2005; Takeuchi et al., 2001). Although individual differences in chronotype may contribute to the development and maintenance of sleep problems in prepubertal children, assessment of this construct has been hindered by lack of appropriate, reliable, and valid measures.

Based upon the previous work of Roenneberg and colleagues (Roenneberg et al., 2004; Roenneberg, Wirz-Justice, & Merrow, 2003; Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005) and Carskadon and others (Carskadon, Vieira, &

Acebo, 1993), we developed the Children's Chronotype Questionnaire (CCTQ). The CCTQ is a 27-item mixed-format parent-report scale that provides three individual measures of chronotype in 4- to 11- year-old children: MSF, a multi-item morningness/eveningness scale (M/E), and a 5-point chronotype item (CT). The purpose of this study was (1) to describe prepubertal children's chronotypes as assessed by these three individual measures; (2) to examine concordance (validity) between children's chronotype measures and sleep/wake parameters (parental reports and actigraphic estimates); (3) to assess associations between the three children's chronotype measures; and (4) to examine test-retest reliability of chronotype measures and sleep/wake parameters.

## METHODS

### Subjects

Children were recruited as part of three individual studies in the greater Zurich area of Switzerland. In the first two studies, researchers recruited 135 children from 34 of 270 Zurich kindergartens (children attend kindergarten for 2 years between 4 and 7 years of age for about 4 hours per day with school start times between 8:15 and 8:30 a.m.). Of these children, 117 children were enrolled and included in the data analysis. The first study was carried out in 2006/2007 [see (Werner, Molinari, Guyer, & Jenni, 2008)], and the second study was completed in 2008. In the third study, 46 children were recruited from primary schools in the greater Zurich area (children attend primary school about 6 hours per day on 5 days per week, starting between 7:45 and 8:15 a.m.) and from a special school program for gifted children; thirty-five of these children were included in this analysis (n=19 recruited from primary schools; n=16 recruited from school program for gifted children). In total, parents of 179 children agreed to participate after initial contact and 152 children were selected for the analysis [75 girls and 77 boys, mean age 6.70 ± 1.5 (SD) years, range = 4-11 years]. At time of assessment, 80 children (53%) were the eldest sibling or an only-child, and 72 children (47%) had an older sibling. None of the children took regular naps.

Overall, 29 children were excluded because (1) parents had insufficient language skills or the questionnaire was not filled out completely (n=12); (2) several families reported data for two or more children, but only one child was included in the data analysis based upon random selection (n=16); and (3) children had a

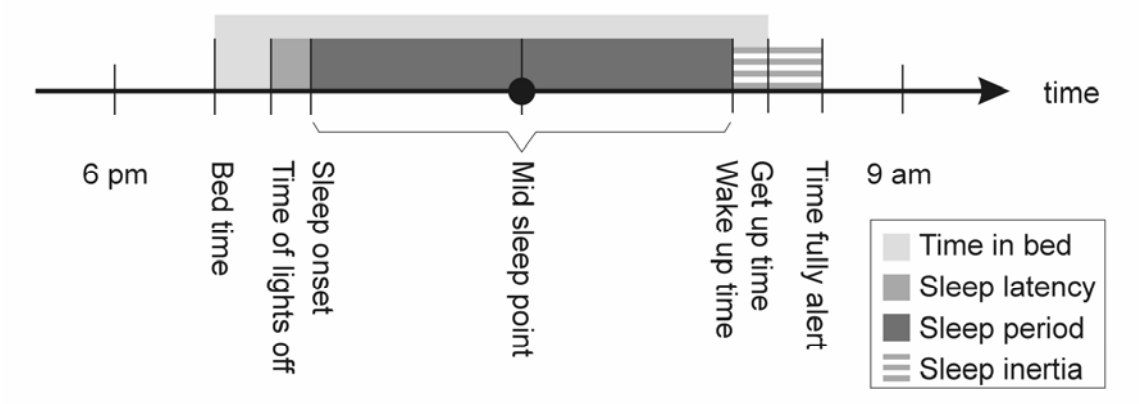
self-reported pubertal development score ≥ 3 (n=1) (Carskadon & Acebo, 1993). The actigraphic validity analysis included data from a sub-sample of 85 children (50 kindergarten and 35 primary school children). These parents filled out the questionnaire prior to actigraphy monitoring, and devices were sent back by postal mail. The test-retest reliability analysis was performed on a sub-sample of 43 children whose parents received and returned questionnaires on two occasions by postal mail.

All families agreeing to participate received a letter including a description of the study and a study enrolment form. The study procedure was explained by the researchers, and written informed consent was obtained from all parents. Families participating in either of the first two studies (see above) were rewarded with a gift certificate from a book shop. All studies were approved by the local research ethics committee, were performed according to the Declaration of Helsinki, and met the ethical standards of this journal (Portaluppi, Touitou, & Smolensky, 2008).

**Measures**

**The Children's ChronoType Questionnaire (CCTQ; see Appendix)**: The CCTQ is an adaptation of the Munich ChronoType Questionnaire (MCTQ, Roenneberg et al., 2004) and the Morningness/Eveningness Scale for Children (MESC, Carskadon, Vieira, & Acebo, 1993). The CCTQ includes a short demographics section about age, sex, birth order, family size, and education level. Parents respond to a number of open-ended questions about sleep/wake parameters for both scheduled and free days (bed time, time of lights-off, sleep latency in minutes, wake up time, get up time, time fully alert). Scheduled days (SC) are defined as those when children's sleep/wake patterns are directly influenced by individual or family activities (e.g., school, athletics). Free days (FR) are defined as those when children's sleep/wake patterns are "free" from any influence of individual or family activities. Computed variables included (see Figure 2-1): (a) *time in bed* defined as the difference between bed time and get up time; (b) *sleep onset* defined as sleep latency added to time of lights-off; (c) *sleep period* defined as the difference between sleep onset in the evening and wake up time in the morning; (d) *sleep inertia* defined as the difference between wake up time and time being fully alert; and (e) *mid sleep point* defined as sleep onset + sleep period/2.

Figure 2-1: Parent-reported sleep/wake parameters computed from items on the Children's ChronoType Questionnaire (CCTQ).




The CCTQ includes three different parent-report measures of children's chronotype: (1) *Mid sleep point on free days (MSF)* -- the MSF is computed as the mid point of the sleep period only on free days. As many individuals compensate for a sleep deficit accumulated during scheduled days by sleeping in on free days (sleep deficit acting as a confounder for sleep period on free days), Roenneberg corrected MSF for the confounding sleep deficit based on the individual weekly average sleep need (*MSFsc*). The average sleep need is defined as (5*sleep period on scheduled days + 2*sleep period on free days)/7 [for correction algorithm for MSF, see supplement to (Roenneberg et al., 2004)]; (2) *Morningness/Eveningness (M/E)* -- the M/E scale score is derived from responses to 10 questions (see Appendix items 17-26) about preferred timing of going to bed, getting up in the morning, taking a cognitive test, and doing physical activities, as well as the child's most prevalent behaviour in recent weeks (e.g., sleepiness after awakened in the morning and in the evening). M/E scale-scores range from 10 (extreme morningness) to 49 (extreme eveningness). Morning-types are classified by a M/E scale score of ≤ 23, intermediate-types by a score of 24-32, and evening-types by a score ≥ 33. Cronbach's Alpha for the 10 items (.81) was similar to that for the adolescent version of Carskadon and colleagues (Carskadon, Vieira, & Acebo, 1993); corrected item-total correlations were on average .49 and ranged from .31 to .71. (3) *Chronotype (CT)* -- the CT is a single item measure. Parents read a short description of different chronotypes and select one of five categories that best represent their child's circadian phase preference (i.e., definitely a morning type, rather a morning type than an

evening type, neither nor type, rather an evening type than a morning type, or definitely an evening type). CT scores range from 1 (definitely a morning type) to 5 (definitely evening type). This measure has been widely used in sleep and circadian research [e.g., (Horne & Ostberg, 1976; Roenneberg, Wirz-Justice, & Merrow, 2003)] with response set varying from 3 to 7 categories.

**Pubertal development**: All children were assessed by the self-rating scale for pubertal development (Carskadon & Acebo, 1993). The scale is an adaptation of the interview-based puberty rating scale by Peterson (Peterson, 1984), including five items for rating physical development, an overall maturation measure, and a categorical maturation score designed to be similar to Tanner staging categories (Tanner, 1962). The puberty scores are categorized separately for girls and boys as 1) pre-pubertal, 2) early pubertal, 3) mid-pubertal, 4) late pubertal, and 5) post-pubertal. Children with a pubertal score ≥ 3 were excluded from this data analysis, because sleep regulatory mechanisms change during the course of puberty (Carskadon, Vieira, & Acebo, 1993).

**Actigraphy:** A total of 85 children were monitored continuously at home with an actigraph (AW4, Actiwatch Plus®, Cambridge Neurotechnology, Cambridge, UK) for 6 to 14 consecutive nights and days (median = 8). Data were analyzed in 1-minute epochs and translated into sleep measures by the software Actiware 5® using the scoring procedures described by Acebo (2005). The scoring interval was defined as 30 minutes before the reported bedtime to 30 minutes after the reported rising time. Data were evaluated at a medium-sensitivity threshold. Actigraphic sleep measures for the analysis included: (1) *Bed Time* as indicated in the diary; (2) *Sleep Start Time* defined as the first minute of at least 3 consecutive minutes of scored sleep after bed time; (3) *Sleep End Time* as the last minute of at least 5 consecutive minutes of scored sleep just prior to the reported rise time; (4) *Assumed Sleep* ("nocturnal sleep period") as the difference between Sleep Start Time and Sleep End Time; (5) *Sleep latency* defined as the difference between Bedtime and Sleep Start Time; and (6) *Mid Sleep Point* defined as Sleep Start Time + Assumed Sleep/2. Actigraphs were attached to the non-dominant wrist of the children and removed only during times when it could get wet. Children were monitored during the academic year, including one or two weekends, but not during school vacation. Data for each

actigraph measure were aggregated (averaged) separately for week-days (scheduled - SC) and weekend-days (free - FR) nights, which were used as the units of analysis. All public vacation days were counted as free days. The total number of monitored nights was 917 (SC range = 4-14; FR range = 1-6). Individual actigraphy nights were discarded if the child was sick (4/917 nights), if the actigraph was off for all or parts of the night (3/917), if parents had forgotten to fill out the diary (9/917), or if the diary indicated unusual external motion that would mask sleep (e.g., sleeping in the car, 2/917).

**Diary:** Parents completed a sleep diary on each study day that sleep was assessed with actigraphy. Diary reports were recorded in 15-minute intervals [e.g., bedtime was indicated by a "greater sign" (>); estimated sleep start and sleep end were noted by starting and ending a continuous line]. Parents also noted any type of activity that may have influenced the scoring of actigraphic data [e.g., illness, intervals the actigraph was off of the child, car rides, see Acebo et al. (2005)]. This diary has been used clinically at our center for several years (Werner, Molinari, Guyer, & Jenni, 2008).

**Statistical Analysis**

Descriptive results are presented as means and standard deviations (SD). Because parents commonly reported their children's sleep/wake times to the nearest full-hour or half-hour rather than to the nearest minute (e.g., 8:15 p.m., rather than 8:07 p.m. bedtime), many variables from the CCTQ had significant skewness and/or kurtosis. As a consequence, we used nonparametric tests for all parameters for testing equality of means (Wilcoxon-Test) and Spearman correlations to measure associations. Simple and quadratic regression (quadratic term was never significant) and analysis of variance were used to describe the relationship between sleep/wake parameters and demographic variables (age, sex, birth order, and type of day). Effect size in SD units (Cohen's d) was computed for actigraphy and questionnaire mean (M) comparisons and for scheduled and free days mean (M) comparisons ($d = M_{sample\ 1} - M_{sample\ 2}/SD_{pooled}$) (Cohen, 1962). Test-retest reliability coefficients were determined with Pearson correlations, except for the chronotype measure CT, which was assessed with Spearman correlations. All analyses were performed with two-tailed tests, and p

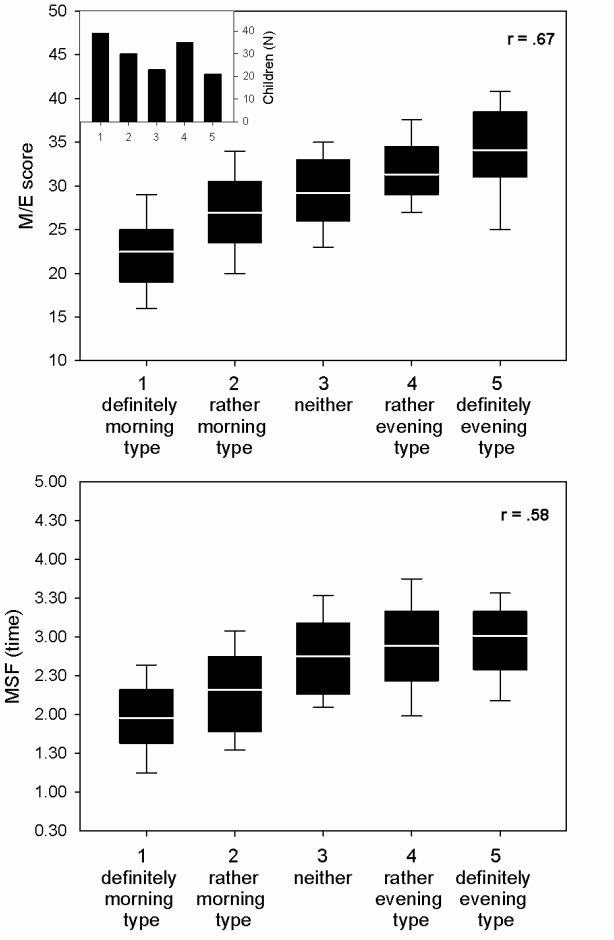
< 0.05 was considered significant. SPSS (14.0J for Windows; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

## RESULTS

### Parental reports of children's sleep / wake parameters on scheduled (SC) and free days (FR)

Descriptive statistics for sleep/wake parameters are shown separately for scheduled and free days in Table 2-1 (parameters are illustrated in Figure 2-2). Mean differences between scheduled and free days were significant for all sleep/wake parameters (Table 2-1). On free days, children went to bed later and got up at later times, slept about 20 minutes longer, and had shorter sleep latencies and sleep inertia estimates than on scheduled days.

Figure 2-2: Distribution of ChronoType (CT) scores (upper left insert) and associations with Morningness/Eveningness (M/E) scores and mid sleep point on free days (MSF).




White line within boxes: median. Lower/upper border of the boxes: interquartile range.

Table 2-1: Descriptive statistics for parent-reported sleep/wake parameters on scheduled and free days from the Children's ChronoType Questionnaire (CCTQ) and linear regression coefficients by age (n=152).

| | Scheduled Days[a] | Free Days[a] | Statistics | Scheduled Days[b] | Free Days[b] |
|---|---|---|---|---|---|
| Bed time | 20:17 (0:31) | 20:47 (0:46) | $p < 0.001$, $d = 0.77$ | 0:09 (0:01) † | 0:16 (0:02) † |
| Time of lights off | 20:35 (0:36) | 21:02 (0:48) | $p < 0.001$, $d = 0.66$ | 0:11 (0:02) † | 0:18 (0:02) † |
| Sleep latency | 0:12 (0:09) | 0:11 (0:10) | $p \leq 0.001$, $d = 0.07$ | 0:01 (0:00:29) | |
| Sleep onset | 20:47 (0:38) | 21:13 (0:50) | $p < 0.001$, $d = 0.59$ | 0:13 (0:02) † | 0:19 (0:02) † |
| Wake up time | 7:07 (0:25) | 7:51 (0:46) | $p < 0.001$, $d = 1.23$ | -0:01 (0:01) | 0:09 (0:02) † |
| Get up time | 7:16 (0:25) | 8:00 (0:48) | $p < 0.001$, $d = 1.20$ | -0:00:04 (0:01) | 0:11 (0:02) † |
| Time fully alert | 7:29 (0:36) | 8:05 (0:53) | $p < 0.001$, $d = 0.81$ | -0:01 (0:02) | 0:10 (0:03) † |
| Sleep period | 10:20 (0:40) | 10:38 (0:45) | $p < 0.001$, $d = 0.43$ | -0:11 (0:02) † | |
| Time in bed | 10:59 (0:34) | 11:14 (0:47) | $p < 0.001$, $d = 0.37$ | -0:10 (0:02) † | -0:05 (0:02) † |
| Sleep inertia | 0:22 (0:23) | 0:14 (0:20) | $p < 0.001$, $d = 0.33$ | 0:01 (0:01) | |
| Mid sleep point | 1:58 (0:26) | 2:32 (0:43) | $p < 0.001$, $d = 1.00$ | 0:06 (0:01) † | 0:14 (0:02) † |
| MSFsc | 2:26 (0:40) | | | 0:13 (0:02) † | |

[a] Reported as mean (standard deviation), in hours : minutes.

[b] Reported as slope coefficient (standard error). When no interaction between age and type of day (scheduled versus free) existed, the common slope was reported (Analysis of Covariance); otherwise separate slopes are reported.

† Significant effect of age ($p \leq .05$).

Because age is a predictor of many sleep/wake parameters, age effects were examined by simple regression [Table 1 reports coefficients of age with standard error (SE)]. Results indicate that older children went to bed later, had later sleep onsets, had shorter sleep periods and spent less time in bed than younger children. Sleep latency and sleep inertia on both types of day (SC, FR) were not influenced by age. Wake up time, get up time, and time fully alert were later for older children on free days only. After controlling for age, girls had longer sleep latencies and woke up later than boys ($p < .05$). Sleep/wake parameters were not associated with birth order.

**Children's chronotype measures**

MSF and MSFsc did not show any significant deviation from a normal Gaussian distribution. Although statistically significant ($p < .001$), MSF and MSFsc means differed by only 6 minutes [.10 hours; MSF = 2.53 (.71) versus MSFsc = 2.43 (.67)], with a small effect size ($d = .15$). MSF and MSFsc were both significantly related to children's age (older children had later MSFs) and sex (girls have later MSFs than boys), but not to birth order. The distribution of the M/E score did not show any significant deviation from normality, with a mean of 28.2 (SD = 6.0; range = 15 to 43). The M/E score was not associated with age, sex or birth order. The distribution of the CT is presented in the inlet of Figure 2. Thirty-nine parents (26%) classified their children as definitely morning type, 30 (20%) as rather morning type than evening type, 23 (15%) as neither nor type, 35 (23%) as rather evening type than a morning type, and 21 (14%) as definitely evening type. Age, sex and birth order were not related to CT.

**Concordance between parental-report of sleep/wake parameters and chronotype measures**

Validity of the three measures of children's chronotype was first examined by determining concordance with sleep/wake parameters (see Table 2-2). All three measures of children's chronotype were significantly related to time going to bed, time of lights off, sleep latency, sleep onset, wake up time, get up time, and time fully alert. Across chronotype measures, the highest correlations were with MSFsc [e.g., for sleep onset (r=.93) and time of lights-off (r=.92) on free days]. Later chronotypes had later sleep start times, later get up times, and later times to be fully alert. While chronotype as measured by M/E or CT was not related to

sleep period on scheduled or free days, chronotype as measured by MSF was related to sleep period on scheduled days (r=-.37), and MSFsc was related to sleep period on both type of days (SC: r=-.32; FR: r=-.24).

As shown in Table 2-1, children significantly delayed their sleep/wake patterns from scheduled to free days (e.g., bedtime for 30 minutes; get up time for 44 minutes) and slept on average 18 minutes longer on free days than scheduled days. We found a positive correlation between the difference in sleep period on scheduled and free days with children's chronotype. Earlier chronotypes extended their sleep period less on free days than later chronotypes (MSF: $r = .33$, $p < .001$; M/E-score: $r = .32$, $p < .001$; CT: $r = .29$, $p < .001$). The difference between sleep period on scheduled and free days was not related to MSFsc ($r = .04$, $p \geq .05$). Furthermore, later chronotypes (all three chronotype measures) had longer sleep inertia on scheduled days, and later chronotypes (M/E and CT measures) reported a longer time in bed on free days than earlier chronotypes (see Table 2-2).

**Relations between chronotype measures**

The three different measures of the children's chronotype were significantly correlated ($r = .52$ to $r= .67$; Table 2). Figure 2-2 illustrates monotonic relationships between CT and the two other chronotype measures (MSF and M/E). While the association between M/E and CT appears to be linear, the association between MSF and the CT suggests a levelling off in the two evening classes (moderate and definitely).

**Parent-reported and actigraphically-estimated sleep/wake parameter comparisons**

On a sub-sample of 85 children, parent-reported sleep/wake parameters were compared to measures derived from actigraphy (Table 2-3). On average, parents reported significantly earlier sleep onsets, later wake up times, and longer sleep periods than estimated by actigraphy. Discrepancies between the two measures (e.g., earlier parental report of sleep onset time and later parental report of wake time as computed by actigraphy) were on average approximately the same. Thus, the finding of no significant differences in mid sleep point on scheduled and free days was not surprising. Parental reports of sleep latency were significantly shorter than corresponding actigraphic estimates. In contrast,

MSFsc computed from actigraphic measures was 12 minutes later than from the CCTQ (p = .006, *d* = .27).

Table 2-2. Spearman correlations between parent-reported sleep/wake parameters and mid sleep point on free days (MSF), corrected mid sleep point on free days (MSFsc), morningness/eveningness (M/E) scores and chronotype (CT) scores (n=152).

| | | MSF | MSFsc | M/E-score | CT |
|---|---|---|---|---|---|
| Bed time | SC | 0.59* | 0.57* | 0.33* | 0.23* |
| | FR | 0.76* | 0.82* | 0.31* | 0.31* |
| Time of lights off | SC | 0.68* | 0.64* | 0.43* | 0.36* |
| | FR | 0.86* | 0.92* | 0.40* | 0.40* |
| Sleep latency | SC | 0.31* | 0.31* | 0.23# | 0.29* |
| | FR | 0.18# | 0.19# | 0.25# | 0.29* |
| Sleep onset | SC | 0.70* | 0.66* | 0.46* | 0.41* |
| | FR | 0.87* | 0.93* | 0.42* | 0.45* |
| Wake up time | SC | 0.46* | 0.45* | 0.52* | 0.40* |
| | FR | 0.89* | 0.75* | 0.63* | 0.59* |
| Get up time | SC | 0.51* | 0.47# | 0.55* | 0.41# |
| | FR | 0.87* | 0.75* | 0.63* | 0.57* |
| Time fully alert | SC | 0.53* | 0.48# | 0.68* | 0.50* |
| | FR | 0.82* | 0.69* | 0.66* | 0.59* |
| Sleep period | SC | -0.37* | -0.32* | -0.12 | -0.18 |
| | FR | -0.05 | -0.24# | 0.16 | 0.13 |
| Time in bed | SC | -0.16 | -0.16 | 0.11 | 0.06 |
| | FR | 0.08 | -0.09 | 0.29# | 0.22# |
| Sleep inertia | SC | 0.28* | 0.21# | 0.45* | 0.27* |
| | FR | -0.00 | -0.03 | 0.28* | 0.10 |
| M/E-score | | 0.584* | 0.516* | | 0.672* |
| CT | | 0.581* | 0.524* | 0.672* | |

Note: Correlation coefficients are reported for scheduled (SC) and free (FR) days.

* p ≤ .001; # p ≤ .05

Table 2-3. Comparison of actigraphic estimates of sleep/wake parameters and corresponding parent reports from the Children's ChronoType Questionnaire (CCTQ; n=85).

| | Actigraphy | | CCTQ | | Statistics | |
|---|---|---|---|---|---|---|
| | Scheduled Days[a] | Free Days[a] | Scheduled Days[a] | Free Days[a] | Scheduled Days* | Free Days[#] |
| Bed Time/ Time of Lights-Off | 20:49 (0:43) | 21:31 (0:57) | 20:41 (0:40) | 21:13 (0:55) | $p < 0.01$, $d = 0.19$ | $p<0.001$, $d = 0.32$ |
| Sleep Start / Sleep onset | 21:08 (0:42) | 21:51 (0:56) | 20:55 (0:43) | 21:25 (0:58) | $p < 0.001$, $d = 0.32$ | $p<0.001$, $d = 0.46$ |
| Sleep End/ Wake up time | 7:00 (0:26) | 7:42 (0:44) | 7:08 (0:28) | 7:57 (0:50) | $p < 0.01$, $d = 0.29$ | $p<0.001$, $d = 0.32$ |
| Assumed Sleep/Sleep period | 9:49 (0:38) | 9:55 (0:40) | 10:13 (0:43) | 10:32 (0:50) | $p < 0.001$, $d = 0.59$ | $p<0.001$, $d = 0.83$ |
| Sleep Latency | 0:20 (0:11) | 0:20 (0:14) | 0:14 (0:10) | 0:12 (0:11) | $p < 0.001$, $d = 0.56$ | $p<0.001$, $d = 0.68$ |
| Mid Sleep Point | 2:03 (0:31) | 2:48 (0:47) | 2:01 (0:29) | 2:40 (0:48) | NS | NS |
| MSFsc | 2:46 (0:47) | | 2:34 (0:46) | | $p < 0.01$, $d = 0.27$ | |

[a] Reported as mean (standard deviation), in hours : minutes.

* *Wilcoxon* Signed-Rank -Test between actigraphy and questionnaire data for scheduled days.

[#] *Wilcoxon* signed-Rank -Test between actigraphy and questionnaire data for free days.

NS: not significant.

**Concordance between actigraphic estimates of sleep/wake parameters and chronotype measures**

Validity of chronotype measures was also assessed by examining concordance between actigraphically estimated sleep/wake parameters (SC and FR) and the three chronotype measures. Spearman correlations are presented in Table 2-4. Independent of type of day (SC, FR), later chronotypes had later bedtimes, sleep

start times, and sleep end times. Sleep latency as assessed by actigraphy was not significantly related to any parent-report measure of children's chronotype. Assumed sleep assessed by actigraphy was negatively related to the MSF and MSFsc, but not to M/E or CT. Concordance between parent-reported and actigraphically estimated MSF was high (r = .78; for MSFsc: r = .70)

Table 2-4. Spearman correlations between actigraphic estimates of sleep/wake parameters and parent reports of mid sleep point on free days (MSF/MSFsc), morningness/eveningness scale (M/E) scores, and chronotype (CT) scores (n=85).

| Actigraphy | | Children's ChronoType Questionnaire (CCTQ) | | | |
|---|---|---|---|---|---|
| | | MSF | MSFsc | M/E | CT |
| Bedtime | SC | 0.70** | 0.72** | 0.39** | 0.30* |
| | FR | 0.74** | 0.74** | 0.44** | 0.40** |
| Sleep latency | SC | 0.05 | -0.03 | 0.003 | 0.01 |
| | FR | -0.04 | -0.05 | 0.09 | 0.15 |
| Sleep Start | SC | 0.70** | 0.70** | 0.41** | 0.32* |
| | FR | 0.75** | 0.74** | 0.45** | 0.43** |
| Sleep End | SC | 0.46** | 0.45** | 0.45** | 0.34* |
| | FR | 0.64** | 0.56** | 0.65** | 0.51** |
| Assumed Sleep | SC | -0.49** | -0.51* | -0.10 | -0.10 |
| | FR | -0.31* | -0.38** | 0.05 | 0.00 |
| Mid Sleep Point | SC | 0.67** | 0.66** | 0.50** | 0.37** |
| | FR | 0.78** | 0.73** | 0.57** | 0.50** |
| MSFsc | | 0.73** | 0.70** | 0.52** | 0.47** |

Note: SC = scheduled days; FR = free days.

* $p \leq .05$ ; ** $p \leq .001$

**Test-retest reliability**

The CCTQ was administered twice within 2-4 weeks (range between the two administrations: 14 - 37 days, mean=20 days) to parents of 46 children (23

girls, 50%) who were on average 7.7 years old (range: 4.4-11.0 years). Standard deviations for the sleep/wake parameters of the first and second administration were approximately the same, and mean differences between the two administrations were not significant for any parameter ($p > .05$). The reliability was moderate-to-high for most sleep/wake parameters ($r = .58$ to $r = .94$, Table 2-5) and high for the three chronotype measures [$r = .91$ ($p < .001$) for MSF; $r = .79$ ($p < .001$) for MSFsc; $r = .94$ ($p < .001$) for M/E; and $r = .84$ ($p < .001$) for CT]. The time between the two administrations and whether the questionnaires had been filled out on the same type of day (e.g., both on scheduled, or free) did not significantly influence differences between the two administrations.

Table 2-5. Test- Retest Reliability (Pearson correlations) within 2-4 weeks for parent-reported sleep/wake parameters, mid-sleep point on scheduled and free days, and corrected mid sleep point on free days (MSFsc; n=46).

| | Scheduled days | Free days |
|---|---|---|
| Bedtime | 0.90 | 0.88 |
| Time of lights-off | 0.90 | 0.85 |
| Sleep latency | 0.74 | 0.58 |
| Sleep onset | 0.92 | 0.85 |
| Wake up time | 0.89 | 0.91 |
| Get up time | 0.91 | 0.91 |
| Time fully alert | 0.94 | 0.89 |
| Sleep period | 0.94 | 0.79 |
| Time in bed | 0.92 | 0.82 |
| Sleep inertia | 0.78 | 0.70 |
| Mid Sleep Point | 0.87 | 0.91 |
| MSFsc | 0.79 | |

All correlations $p \leq .001$. Note: Reliability coefficients for M/E and CT presented in text.

## DISCUSSION

This study describes the assessment of chronotype in children between 4 and 11 years of age using three different measures: the Mid Sleep point on Free days (MSF), the Morningness/Eveningness scale (M/E) score, and a 5-point Chronotype (CT) score. To our knowledge, no parent-report questionnaire with adequate reliability and validity is available for the assessment of children's chronotype in prepubertal children. We adapted measures of morningness/eveningness used in adolescents and adults [from (Carskadon, Vieira, & Acebo, 1993; Horne & Ostberg, 1976; Smith, Reilly, & Midkiff, 1989)] and combined them with other measures used in the literature (i.e., the MSF and the CT) into a single questionnaire (CCTQ). This study provides validity data for the CCTQ using actigraphy, as well as 2-4 week test-retest reliability data. Overall, findings indicate moderate to strong agreement between the three chronotype measures, adequate associations between sleep/wake parameters (parent-report and actigraphy) and chronotype measures, and excellent temporal stability for all three chronotype measures (reliability).

Comparisons between the three chronotype measures and parental reports of sleep/wake parameters suggest stronger relations between sleep/wake parameters and MSF/MSFsc than between sleep/wake parameters and M/E or CT. Higher correlations with MSF/MSFsc may be explained by the fact that these measures are computed derivations of reported sleep onset and sleep period, while assessment of M/E and the CT require methodologically distinct responses from parents. The M/E score is a sum score of multiple items measuring children's "best" time to sleep, take a cognitive test, and do physical activities, as well as children's level of sleepiness at different times of the day. Likewise, the CT is an overall parental impression of children's chronotype using five response choices. Our results indicate that later chronotypes as measured by MSF/MSFsc, M/E, and CT are more likely to have later bed times, lights-off times, and sleep onset times, longer sleep latencies, later wake up and get up times, and take longer to be fully alert in the morning than earlier chronotypes (independent of type of day). These findings are consistent with previous reports on circadian preference with adolescents and adults [e.g. (Carskadon, Vieira, & Acebo, 1993; Roenneberg, Wirz-Justice, & Merrow, 2003)], suggesting that the CCTQ adequately measures chronotype in prepubertal children.

The validity of parent-reported sleep/wake parameters and chronotype measures was examined by objective data (actigraphy). The relationship between bed time, sleep onset, wake up time, and children's chronotype was verified with estimates from actigraphy. The finding that sleep latency was significantly related to children's chronotype was not verified with estimates from actigraphy. This may due to parents' difficulty in providing accurate estimates of sleep latency, especially for later chronotypes (i.e., children's sleep onset is later than their parents') or for children who require little-to-no assistance in falling asleep at bedtime. While many sleep/wake parameters significantly differ between actigraphy and questionnaire data, mid sleep point on scheduled and free days did not. This finding indicates objective validity for the chronotype measure MSF. The significant discrepancies between actigraphy and questionnaire data in sleep/wake parameters are well documented in the literature (Acebo et al., 2005; Sadeh, Lavie, & Scher, 1994; Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991; Werner, Molinari, Guyer, & Jenni, 2008) and may be explained by methodological differences (e.g., actigraphy estimates sleep/wake patterns based on movements during specified time intervals while subjective reports may be influenced by recall, experiences, and expectations and are not primarily based on a particular time window).

Relations between the three different chronotype measures (MSF/MSFsc, M/E, and CT) were moderate-to-high. The strongest correlation was between M/E and CT, which may be explained by the sequence of filling out the CT after the two other measures. That is, parents may have become more in tune with the chronotype construct after completing questions resulting in MSF and M/E. High correlations between M/E scores and CT have been also reported in adult populations by Roenneberg [r= -.80; chronotype self-assessment on a 7-point scale (Roenneberg et al., 2007)].

Although the correlations between the three different chronotype measures in our study were moderate-to-high, some incorrect classifications of morning types as evening types and vice versa may have occurred. Comparing for example the M/E- and CT-scores classified into three groups (morning-types, intermediate-types, and evening-types), our data may suggest that extreme misclassifications were rare. Because an honest false classification rate can not be provided by our analysis, further studies should compare parent-reported chronotype measures

with physiological circadian parameters (e.g., dim light melatonin onset), which may provide additional validity data for classifying children's chronotype.

The test-retest analysis of sleep/wake parameters and the three chronotype measures suggests excellent temporal stability. A test-retest period of 2-4 weeks was chosen according to Knapp & Brown (1995) who showed that a time period of 2-4 weeks is not too short (the shorter the interval, the more answers of the first administration may be recalled and thereby producing an artificially high estimate of the instrument), and not too long (the longer the interval, the more likely the true scores may have changed). The reliability coefficient for sleep latency and sleep inertia was influenced by two individual subjects for whom the difference between the 2 administrations was about half an hour (range of remaining values: -0.25 to 0.33). When these subjects were discarded from the analysis, the correlation was higher. We cannot distinguish whether the moderate test retest correlation of sleep latency and sleep inertia is due to more variability of the child's behaviour (e.g., difficulty falling asleep due to stressful events) or to less reliability of the parent report (e.g., if children do not need parents assistance to fall asleep).

Data from many reports in adolescents and adults show that individuals delay their sleep on average by 1-3 hours from scheduled to free days and sleep longer during free days, which has been interpreted as an accumulated sleep deficit [e.g., (Carskadon, Vieira, & Acebo, 1993; Roenneberg et al., 2004)]. These findings prompted Roenneberg and colleagues to correct MSF for the accumulated sleep deficit during the work week [see Appendix in (Carskadon, Vieira, & Acebo, 1993; Roenneberg et al., 2004)]. Our data indicate that the delaying pattern is already evident in prepubertal children, although to a lesser degree than in older children and adults. We found that prepubertal children delay on average their sleep onset for 26 minutes and wake up time for 44 minutes and therefore sleep 18 minutes longer on free days than on scheduled days. Compared to Wolfson & Carskadon (1998), 15-year-old adolescents go to bed 106 minutes later and get up 220 minutes later on weekends, oversleeping 114 minutes. The age effect on sleep/wake patterns [e.g. (Carskadon, Wolfson, Acebo, Tzischinsky, & Seifer, 1998; Iglowstein, Jenni, Molinari, & Largo, 2003; Randler, 2008a)] is likely influenced by environmental factors (e.g., increasing night time activity and setting their own bedtimes) and biological factors (e.g., maturation of the circadian system and the sleep/wake homeostatic regulatory

processes (Carskadon, Vieira, & Acebo, 1993; Jenni, Achermann, & Carskadon, 2005; Jenni & LeBourgeois, 2006). As a consequence, we corrected MSF for the accumulated sleep deficit as suggested by Roenneberg (2004).

We note that the study participation was voluntary, and the study population represents a small community sample, with an imbalance between the number of children aged 4-7 and those aged 7-11 years. Furthermore, we did not collect concurrent self-reported data from school children, and parents were not asked to report sleep/wake parameters to specified precision (e.g., 5 or 10 minutes), which may have resulted in significant deviation from normality for many sleep/wake parameters. Although this study presents findings in need of replication (also in different cultural groups [(e.g., Caci et al., 2005)], we still believe that the CCTQ is a convenient, brief, and easy-to-administer questionnaire providing three different chronotype measures. Which of these measures may be recommended for clinical or research use depends on particular questions and aims.

Our results indicate that 4- to 11-year-old children already delay their sleep/wake patterns and "oversleep" about 15 minutes between scheduled and free days. As a result, prepubertal children, especially those with later chronotype classifications, may have difficulties obtaining sufficient sleep. Because eveningness is associated with increased daytime sleepiness, greater emotional, attentional, and behavioral problems, and poorer school achievement, knowing the individual's circadian phase preference may help the clinician dealing with these difficulties. We propose that the CCTQ be used in future studies, including those with clinical populations (e.g., sleep disorders, learning disorder, behavioral problems). We conclude that the all three measures included in the CCTQ (MSF, M/E and CT) are equally valid and reliable measures for the assessment of chronotype in prepubertal children between 4 and 11 years of age.

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**APPENDIX**

**Children's ChronoType Questionnaire (CCTQ)**

**Demographics:** Please answer the following questions or choose the best answer.

Individual completing the questionnaire: ☐ Mother ☐ Father ☐ Other _____

Today's Date: ___ / ___ / ____ (day/month/year) Child's Sex: ☐ Male ☐ Female

Child's Birth Date: ___ / ___ / ____ (day/month/year) Child's Birth Order: _____ Is he/she an Only Child? ☐ Yes ☐ No

Child's Age: _____ years

How many children are included in your nuclear family? _____

Do all children in your family have the same biological parents? ☐ Yes ☐ No

Child's current level of education:

☐ Preschool ☐ Kindergarten ☐ Grade _____ ☐ Not attending school

If he/she attends school, how many days/week? _____ How many hours/day? _____

Does he/she go to Day Care or After-School Care? ☐ Yes ☐ No

If yes, how many days/week? _____ How many hours/day? _____

*Directions*: The following questions ask about sleep/wake patterns during "Scheduled Days" in contrast to "Free Days". Think about your child's behavior during recent weeks when answering these questions. For questions with changing conditions (e.g., child goes to day care at 7:00am 1 day/week and 9:00am 3 days/week), fill in or select the most frequent or common answer.

**Scheduled Days**

Child's sleep-wake pattern is directly influenced by individual or family activities (e.g., by school, day care, work, athletics etc.)

On Scheduled Days, my child …

1. …wakes up at _____ : _____ am

2. …regularly wakes up: ☐ by him/herself ☐ with help from a family member ☐ with an alarm clock

| | |
|---|---|
| 3. | …gets up at _____ : _____ am |
| 4. | …is fully awake by _____ : _____ am |
| 5. | …takes regular naps: ☐ Yes ☐ No<br>If yes, he/she naps ___ days/week.<br>If yes, he/she sleeps for ___ minutes/nap.<br>If no, why does he/she not nap? _____ |

On nights before Scheduled Days…

| | |
|---|---|
| 6. | …my child goes to bed (body in bed) at _____ : _____ pm |
| 7. | …my child is ready to fall asleep (lights turned out) at _____ : _____ pm |
| 8. | …it takes him/her _____ minutes to fall asleep (after lights turned out). |

**Free Days**

Child's sleep/wake pattern is "free" from the influence of individual or family activities

(e.g., by school, day care, work, athletics etc.)

On Free Days, my child …

| | |
|---|---|
| 9. | …normally wakes up at _____ :_____ am |
| 10. | …wakes at his/her normal time on scheduled days, but then goes back to sleep after waking: ☐ Yes ☐ No If yes, my child goes back to sleep for _____ minutes after waking. |
| 11. | …gets up by _____ : _____ am |
| 12. | …is fully awake by _____ : _____ am |
| 13. | …takes regular naps: ☐ Yes ☐ No<br>If yes, he/she naps ___ days per week.<br>If yes, he/she sleeps for ___ minutes per nap.<br>If no, why does he/she not nap? _____ |

On nights before Free Days…

| | |
|---|---|
| 14. | …my child goes to bed (body in bed) at _____ : _____ pm |
| 15. | …my child is ready to fall asleep (lights turned out) at _____ : _____ pm |
| 16. | …it takes him/her _____ minutes to fall asleep (after lights turned out). |

*Directions*: For each of the following questions, please select the answer that best describes your child. Make your judgments based on how the behavior of your child was in recent weeks. There are no "right" or "wrong" answers.

| | |
|---|---|
| 17. | *If your child has to be awakened, how difficult do you find it to wake your child up in the morning?<br>a. very difficult b. fairly difficult c. moderate difficult d. slightly difficult<br>e. not at all difficult/my child has never to be awakened |
| 18. | *How alert is your child during the first half hour after having awakened in the morning?<br>a. not at all alert b. slightly alert c. moderate alert d. fairly alert e. very alert |
| 19. | Considering your child's "feeling best" rhythm, at what time would your child **get up** if he/she could decide by him/herself and if he/she were entirely free to plan the day (e.g., vacation)?<br>a. prior to 6:30 am b. 06:30 - 7:14 am c. 7:15 - 9:29 am d. 9:30 - 10:14 am<br>e. after 10:15 am |
| 20. | Considering your child's "feeling best" rhythm, at what time would your child **go to bed** if he/she could decide by him/herself and if he/she were entirely free to plan the next day (e.g., weekend)?<br>a. prior to 18:59 pm b. 19:00 - 19:59 pm c. 20:00 - 21:59 pm d. 22:00 - 22:59 pm<br>e. after 23:00 pm |
| 21. | Let's assume that your child has to be at peak performance for a test that will be mentally exhausting for 2 hours. Considering your child's "feeling best" rhythm and that you are entirely free to plan your child's day, which ONE of the three time intervals would you choose for the test?<br>a. 07:00 – 11:00 am b. 11:00 am – 15:00 pm c. 15:00 – 20:00 pm |
| 22. | Let's assume that you have decided to enroll your child in an athletic activity (e.g., swimming). The only class available meets twice a week at 7 to 8 am. How do you think he/she will perform?<br>a. would be in very good form b. would be in good form c. would be in reasonable form<br>d. would find it difficult e. would find it very difficult |
| 23. | At what time in the evening does your child seem tired and in need of sleep?<br>a. prior to 18:30 pm b. 18:30 - 19:14 pm c. 19:15 - 21:29 pm d. 21:30 - 22:14 pm<br>e. after 22:15 pm |
| 24. | *If your child had to get up every day at 6 am, what do you think it would that be like for him/her?<br>a. very difficult b. rather difficult c. moderate difficult<br>d. a little difficult, but not a great problem e. not at all difficult |

25. *If your child always had to go to bed at ___, what do you think it would be like for him/her? (for 2 years old: 06:00 pm; for 2 to 4 years old: 06:30 pm; for 4 to 8 years old: 07:00 pm; for 8 to 11 years old: 07:30 pm)

a. very difficult b. rather difficult c. moderate difficult

d. a little difficult, but not a great problem e. not at all difficult

---

26. When your child wakes up in the morning, how long does it take to be fully awake?

a. 0 minutes (i.e., immediately) b. 1 to 4 minutes c. 5 to 10 minutes d. 11 to 20 minutes

e. ≥ 21 minutes

---

*Directions*: After answering the above questions, you may have a feeling which "Chronotype" or "Time-of-Day type" your child is. For example, if your child would like to sleep quite a bit longer on "Free Days" compared to "Scheduled Days" or if it is difficult for your child to get out of bed on Monday mornings, then he/she is more likely to be an Evening Type person (a "Night Owl"). If your child, however, regularly wakes up and feels perky once he/she gets out of bed, and your child prefers to go to bed rather early than late, then he/she is more likely a Morning Type person (a "Morning Lark"). Please categorize your child using one of the following choices. Please choose only one category!

---

27. My child is…

☐ Definitely a Morning Type

☐ Rather a Morning Type than an Evening Type

☐ Neither a Morning nor an Evening Type

☐ Rather an Evening Type than a Morning Type

☐ Definitely an Evening Type

. ☐ I do not know

---

The M/E score is derived by adding points from answers 17-26 (a=1, b=2, c=3, d=4, d=5), except as indicated by *, where point values has to be reversed.

**Addendum: Intellectual ability and chronotype**

In a cross-sectional study including 420 adults, small but consistent associations between chronotype and intelligence scores in two multiple aptitude batteries (ASVAB: Armed Services Vocational Aptitude Battery (Murphy & Davidshofer, 1998), CAM-IV: Cognitive Abilities Measurement Battery (Kyllonen, 1994)) were reported. Individuals scoring high in eveningness were more likely to score higher in memory, processing speed and several other sub-tests of the two test batteries (Roberts & Kyllonen, 1999). Yet, cognitive testing of this study has been performed during the morning hours, between 8 a.m. and noon.

The authors suggest that evening types may be in a better position to work till late evening which is a prerequisite for today's work environment. Those that are less capable of adapting to late work schedules, namely the morning types would rather be handicapped. They further argue that control of fire for lighting may have been the most important accomplishment for the emerging Homo sapiens. Thus, individuals able to adapt to evening schedules would finally increase their fitness in an evolutionary sense (Roberts & Kyllonen, 1999).

The reported advantage for evening types has further been specified by unpublished reports (student projects). Applying two different tools for the assessment of chrontype (LOCI: Lark-Owl Chronotype Inventory (Roberts & Irvine, 1998) and SWPAQ: Sleep-Wake Pattern Assessment Questionnaire (Verevkin, Putilov, Donskaya, & Putilov, 2008)) and differentiating between fluid and crystallized intelligence, eveningness as determined by either chronotype instrument was again associated with higher scores of intelligence, in particular in fluid IQ measures.

In general, little is known about children's circadian behavior and its relationship with cognitive variables. Thus, up to now, it is not known whether the reported advantage for evening types is already present in childhood.

In our study population of 60 healthy children (34 male), aged 7.5 to 11.2 years old (mean age=9.4 years, SD=1.0), three different measures for circadian phase preference ("chronotype") have been used: the 5-point chronotype (CT) score, the mid-sleep point on free days (MSF) and the morningness-eveningness (M/E) score (see fig. 2-3).

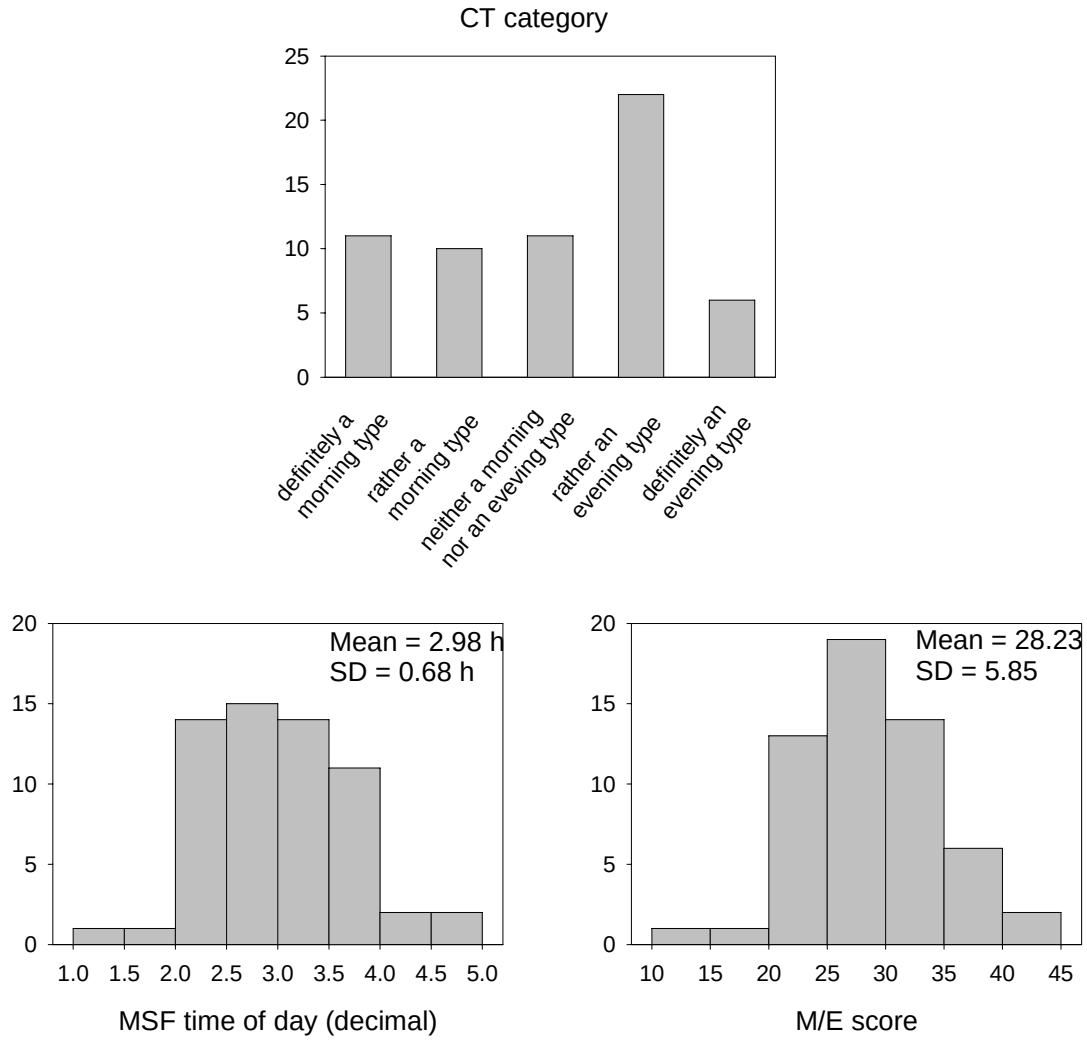
The CT is a single item measure, consisting of the selection one of five categories that best represent the circadian phase preference (i.e., *definitely a morning type, rather a morning than an evening type, neither a morning nor an evening type, rather an evening than a morning type*, or *definitely an evening type*).

The MSF is computed as the mid point of the sleep period on free days (half of the sleep duration added to the sleep start).

The M/E score is derived from responses to 10 questions about preferred timing of going to bed, getting up in the morning, taking a cognitive test, and doing physical activities. M/E scale scores range from 10 (extreme morningness) to 49 (extreme eveningness). For details on the different measures see study II (Werner, Lebourgeois, Geiger, & Jenni, 2009).

All three circadian scores have been analysed and tested seperately for their potential association with cognitive variables (full scale IQ score, verbal IQ, fluid IQ, working memory, speed of processing).

Figure 2-3: Distribution (number of children) of children's Chronotype. Upper panel: chronotype assessed as the chronotype (CT) score. Lower left panel: chronotype assessed as the mid-sleep point on free days (MSF). Lower right panel: chronotype assessed as the morningness-eveningness (M/E) score. N=60




To evaluate the relationship between the 5-point chronotype (CT) score (group variable) and scores of each cognitive index as dependent variable (*full scale IQ*, *verbal IQ*, *fluid IQ*, *working memory* and *speed of processing*) one-way analyses of variance (ANOVAs) were carried out (total study population, N=60). The independent variable, the CT score, consisted of five categories: *definitely a morning type*, *rather a morning type*, *neither a morning nor an evening type*, *rather an evening type*, *definitely an evening type*. None of the ANOVAs was

significant ($F$(4,57)=.46- 1.91, $p$>.05), thus there was no relationship between scores of the different cognitive indices and chronotype (derived from CT score).
To further explore the relationship between chronotype (CT score) and cognitive variables, a new category was formed, combining those from *definitely morning types* and *rather morning types* (N=22, *morning type*) and another new category was formed from *definitely evening type* and *rather evening type* (N=28, *evening type*). Those children in the category *neither a morning nor an evening type* (N=10) were not included in this explorative analysis. Independent-samples t tests were then performed to investigate whether the two groups (*morning type* vs. *evening type*) score differently on any of the cognitive variables (*full scale IQ, verbal IQ, fluid IQ, working memory* and *speed of processing*). Those children characterized as morning type had higher scores in the speed of processing index ($M_{morning\ types}$=116 (SD=12.8), $M_{evening\ types}$ =107 (SD=13.8), $t$(48)=2.49, $p$<.05). All other cognitive variables did not differ between the two groups.

Partial correlations (controlled for age and SES) were computed among the mid-sleep point on free days (MSF) and the cognitive variables (*full scale IQ, verbal IQ, fluid IQ, working memory* and *speed of processing*) for the total study population (N=60). There was no significant correlation between any of the cognitive variables and the MSF.

Partial correlations (controlled for age and SES) were computed among the morningness-eveningness (M/E) score and the cognitive variables (*full scale IQ, verbal IQ fluid IQ, working memory* and *speed of processing*) for the total study population (N=60). *Speed of processing* correlated with the M/E score ($r$=-.32, $p$=.014), indicating that children with lower M/E score (rather morning type) had higher scores of the speed of processing.

In sum, our study population did not reveal the global advantage for evening types as reported for adults (R. D. Roberts & Kyllonen, 1999). In contrast, there was rather an advantage for morning types, yielding higher scores of speed of processing. However, this effect was only present for the direct comparison of morning and evening types of the CT score (excluding those categorized as *neither a morning nor an evening type*) and for the M/E score, but not for the

MSF. Moreover, none of the other cognitive variables was associated with chronotype measures.

Thus, the results of our children's population are more in line with two other studies in adults (Song & Stough, 2000) and elderly people (Gale & Martyn, 1998), stating that chronotype is unrelated to general intelligence.

A number of reasons may account for the failure to replicate the earlier reported results in adults (Roberts & Kyllonen, 1999): First, only a few children belonged to the category of definitely a morning or definitely an evening type, thus statistical power was rather low. Second, it is not possible to rule out circadian influences, because the cognitive testing session could not be matched with the individual phase preferences of a given child. Consequently, the question cannot be answered whether the reported advantage for evening types in adults is developing secondary in response to today's working requirements or whether effects are simply not revealed because of the small number of subjects and biasing circadian influences. Based on the present data, one may even speculate that during childhood, the situation is the other way around, with morning type children benefiting from their earlier phase preference in the sense that their particular demands in terms of sleep timing are usually well accepted by parents. In addition to the parental demands, early school start and other social requirements clearly favor morning types. Evening type children on the other hand, who are wide awake during later evening hours are often in conflict with parental expectations about bed-times and societal demands (i.e., early school starts). Probably, evening type children may thus live under much greater pressure to adapt their phase preference compared to the morning type children.

Study III

**The sleep EEG as a marker of intellectual ability in school age children**

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**ABSTRACT**

Study Objectives: To investigate the within-subject stability in the sleep EEG (trait-like aspects) and the association between the sleep EEG and intellectual abilities in 9 to 12 year old children.

Design: Intellectual ability (WISC-IV, full scale, fluid, and verbal IQ, working memory, speed of processing) were examined and all-night polysomnography was performed (two nights per subject).

Setting: Sleep laboratory.

Participants: Fourteen healthy children (mean age 10.5±1.0 years; 6 girls).

Measurements and Results: Spectral analysis was performed on artefact-free non-rapid eye movement (NREM) sleep epochs (C3/A2). To determine intra-individual stability and inter-individual variability of the sleep EEG, power spectra were used as feature vectors for the estimation of Euclidean distances and intraclass correlation coefficients (ICC) were calculated for the two nights. Sleep spindle peaks were identified for each individual and individual sigma band power was determined.

Trait-like aspects of the sleep EEG were observed for sleep stage variables and spectral power (within-subject distances smaller than between-subject distances; ICC values ranged from .72 to .96). Correlations between spectral power in individual frequency bins and intelligence scores revealed clusters of positive associations in the alpha, sigma and beta range for full scale IQ, fluid IQ and working memory. Similar as in adults, sigma power correlated with full scale (r=.67) and fluid IQ (r=.65), but not with verbal IQ. Spindle peak frequency was negatively related to full scale IQ (r=-.56).

Conclusions: The sleep EEG during childhood shows high within-subject stability and may be a marker for intellectual ability.

Keywords for indexing: sleep; trait; intelligence; development; childhood, sleep spindle, power density spectra, intraclass correlation coefficient

## INTRODUCTION

A *trait* represents a behavioral or biological disposition which is empirically or statistically established (Allport, 1931) , not specific to certain situations or tasks and fairly stable over time (Chen, Gully, Whiteman, & Kilcullen, 2000) .For instance, intelligence defined as the ability to reason, learn and solve problems is considered a trait, irrespective of the specific situation and characterized by a long-term intraindividual stability (Conley, 1984). Hertzog and Schaie (1986) reported stability coefficients for general intellectual ability over seven years and found that their composite score ranged from .89 to .96 in populations ages between 25 to 67 years. Furthermore, based on studies in mono- and dizygotic twins, a considerably large genetic contribution on intelligence (Deary, Johnson, & Houlihan, 2009), with heritability estimates about 40-50% during childhood and about 80% in adulthood (Baltes, Staudinger, & Lindenberger, 1999) were reported. Several studies have explored the relationship between intelligence and physiological parameters. For example Thatcher et al. (2005), reported correlation coefficients of .60 between intelligence quotient (IQ) scores and a combination of parameters derived from the waking EEG, such as amplitude asymmetry, coherence, relative and absolute power, power ratios and phase delay between a combinations of electrodes within certain regions (Thatcher, North, & Biver, 2005). Overall, the concept of intelligence fits the general definition of a trait from both a psychological and biological perspective.

Human sleep also qualifies for a trait with characteristic individual sleep durations and chronotypes (Tucker, Dinges, & Van Dongen, 2007; Van Dongen, Vitellaro, & Dinges, 2005). It is likely that certain aspects of sleep architecture and regulation are also under genetic control (for recent overviews see (Andretic, Franken, & Tafti, 2008; Cirelli, 2005; Tafti, Maret, & Dauvilliers, 2005). Polysomnographic studies indicated that a significant proportion of the variance in stage 2, stage 4, slow wave sleep, and the density of rapid eye movements in REM sleep are in part genetically determined (Linkowski, Kerkhofs, Hauspie, Susanne, & Mendlewicz, 1989; Merica & Gaillard, 1985). Spectral analyses of the sleep EEG in twins revealed that the sleep EEG is among the most heritable traits in humans (Ambrosius et al., 2008; De Gennaro et al., 2008). For example, heritability for the amount of NREM sleep is estimated at about 50% (Linkowski, 1999). The trait-like stability of sleep stages is surpassed by individual profiles of sleep EEG power spectra (Buckelmüller, Landolt, Stassen, & Achermann, 2006;

De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005). Furthermore, the intraindividual stability of power maps largely exceeded the effects that are evoked by experimental manipulations such as sleep deprivation (Finelli, Achermann, & Borbély, 2001). For instance, spindle frequency activity (SFA or sigma power, i.e. spectral power in the 12- 15 Hz range) is highly variable across, but highly stable within individuals (Scholle, Zwacka, & Scholle, 2007; Werth, Achermann, Dijk, & Borbély, 1997), thus representing a trait or phenotype of a given subject. Based on recent data of sleep EEG recordings in mono- versus dizygotic twins, a heretablity estimate of 96% for NREM sleep power spectra for frequencies between 8 and 16 Hz was found (De Gennaro et al., 2008). The spectral composition of NREM sleep EEG was suggested to be suitable for defining endophenotypes (Ambrosius et al., 2008). Such insights from studies in healthy human subjects and patients with sleep disorders are consistent with investigations in inbred mice, where differences in sleep duration and structure, as well as in the spectral composition of the sleep EEG showed high estimates of heritability (reviewed in Dauvilliers, Maret, & Tafti, 2005; Franken & Tafti, 2003). In summary, the human sleep EEG has consistently been described as a trait-like "fingerprint" characteristic, probably reflecting traits of the underlying brain anatomy (Finelli, Achermann, & Borbély, 2001). However, trait-like characteristics of the sleep EEG have not been examined in children.

Despite the general acceptance of trait definitions for both sleep and intelligence, surprisingly little research is documented about the potential relationship between the two phenomena. Early studies from the 1930s examined the link between sleep and intelligence and found a negative correlation between sleep duration and children's intellectual ability (reviewed in Geiger, Achermann, & Jenni, 2010). In fact, our group recently replicated earlier findings and also reported a negative association between sleep duration and intelligence scores in healthy children (Geiger, Achermann, & Jenni, 2010). The few studies in adults that have attempted to link physiological measures of sleep and scores on intelligence tests focused exclusively on sleep spindles or SFA in association with intelligence scores. There is, however, no study that investigates the relationship between spectral power during sleep and intelligence scores in healthy children. In adults, an increase in SFA was reported in highly gifted subjects compared to controls (Schabus et al., 2008) as well as positive correlations between intelligence scores and the total number of sleep spindles (Fogel, Nader, Cote, &

Smith, 2007). Moreover, Bódizs, (2005) found moderately positive correlations between intelligence scores and the percentage of stage 2 sleep.

From developmental research, it is known that sleep spindle number, density, duration, intra-spindle frequency and local distribution change with age (Nicolas, Petit, Rompre, & Montplaisir, 2001; Scholle, Zwacka, & Scholle, 2007; Tarokh & Carskadon, 2010). However, the precise role and function of sleep spindles in cognitive development is not well understood. Furthermore, it is also not known whether the relationship between sleep spindles and intellectual ability shown in adults may also be present in children. Although there are earlier studies about the relationship between SFA and cognitive ability in developmentally delayed children (Bixler & Rhodes, 1968; Gibbs & Gibbs, 1962), only a single non-clinical study examined the relationship between sleep spindles and intellectual performance during childhood (Busby & Pivik, 1983). In this study, Busby and colleagues (1983) reported significantly more stage 2 sleep in school age children with higher intelligence scores compared to those with scores in the normal range. The study population, however, only included male subjects grouped into a superior and an average IQ group by median split. This approach ignores the continuous distribution of IQ scores in the population which limits generalizability of their results. Furthermore, the authors did not report spectral data.

The aim of the present study was to investigate the reliability of inter-individual differences in the sleep EEG (trait-like aspects) and to identify and characterize a potential relationship between the sleep EEG and intellectual ability in healthy children.

## METHODS

### Participants

Fourteen right-handed healthy children between 9.1 to 12.5 years of age (8 male, 6 female, mean age 10.5 years) participated in this study. Eight children were recruited from primary schools in the greater Zurich area and six from a special school program for gifted children. Our aim was to recruit a study population with the greatest possible variability in intellectual ability. Exclusion criteria were chronic diseases, neurological or psychiatric diagnoses (e.g., attention deficit hyperactivity disorder), sleep disorders or taking medication. Socioeconomic status (SES) was determined using the Largo and Pfister (1989)

scale which combines paternal occupation and maternal education resulting in scores ranging from 2 to 12. In 6 children an upper SES (10-12 points) was observed, while a middle SES was found in 8 individuals (6-9 points). Pubertal development status was assessed with a translated rating scale for pubertal development (Carskadon & Acebo, 1993) filled in by the parents. According to the questionnaire, which is related to Tanner staging, twelve children were prepubertal, and two children were mid-pubertal.

**Cognitive and attentional variables**

The children were assessed with the WISC IV (German version, Petermann & Petermann, 2007), yielding separate indices for fluid intelligence, verbal intelligence, speed of processing and working memory as well as a full scale intelligence quotient (IQ) score. WISC IV scores are standardized scores based on age-referenced normative data with a standardized population mean of 100 and a standard deviation (SD) of 15. A children's test battery for the assessment of attention (KITAP, Zimmermann & Fimm, 1993) was also administered to examine different aspects of attention, including alertness and go/nogo. The alertness subtest of the KITAP provided median and SD of reaction times based on age-referenced normative data. A combined score reflecting mean reaction time and SD was calculated and referred to as alertness with a standardized population mean of 50 and a SD of 10. The go/nogo subtest of KITAP also provided median reaction time with a standardized population mean of 50 and a SD of 10.

To rule out learning effects only children who had not performed any kind of intelligence testing during at least the last two years prior to participation in the study were included.

**Procedure**

The study was approved by the institutional review board of the University Children's Hospital and the Canton of Zurich and was performed according to the Declaration of Helsinki. All families received a detailed study description and provided written informed consent. After information about purpose and procedure of the study, the WISC IV (German version) intelligence test (Petermann & Petermann, 2007) was administered by a trained psychologist (A.G.). The participants then performed the two subtests alertness and go/nogo

of the KITAP (Zimmermann & Fimm, 1993). One week prior to the recordings, parents were instructed to maintain childrens' habitual sleep- wake schedule, and to keep a sleep diary with detailed information about bed and wake-up times, caffeine consumption and medication. Additionally, children were monitored for regular sleep- wake schedules with wrist-worn actigraphs. Daytime sleepiness was assessed by the Pediatric Daytime Sleepiness Score (PDSS, Drake et al., 2003), a sum score combining eight different daytime sleepiness items on a 5-point scale (parent report). All children participated in two recording sessions, separated by one or two weeks. Prior to the sleep recordings, children were instructed to refrain from extraordinary physical activity.

**Sleep recordings**

All sleep recordings were performed at the sleep laboratory of the University Children's Hospital Zurich, starting between 9 p.m. and 10.30 p.m. (habitual bed-time of the subjects) and lasting between 8 and 10h (524 ± 29 min).

All-night polysomnography was recorded by a portable high density EEG system (128 electrodes net, Electrical Geodesic, Inc.). The net included the electrode positions of the 10-20 system. Furthermore, the submental electromyogram (EMG) and the electrooculogram (EOG, 2 bipolar derivations) were recorded. EOG electrodes were placed approx. 1 cm below and above the outer canthus. Data were sampled at 500 Hz (0.01 to 200 Hz).

**Data analysis and processing**

Sleep stages were visually scored in 20-s epochs according to standard criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Analysis was restricted to derivation C3/A2. Data were band-pass filtered (0.1 to 40 Hz; FFT filter) and down-sampled to 250 Hz. EEG power density spectra were calculated for consecutive 20-s epochs (FFTW approach [Matlab, The MathWorks Inc.], Hanning window, averages of five 4-s epochs; frequency resolution 0.25 Hz) and matched with the corresponding sleep stages. Artifacts were excluded on a 4-s basis by visual inspection and semi automatically. Epochs were excluded whenever power in the 20-40 Hz and the SWA band exceeded a threshold based on a moving average determined over twenty 20-s epochs. Average spectra of NREM sleep (N2 and N3) were calculated for the minimum common length (6.41 h) of sleep.

Because of technical artefacts affecting electrode A2, the derivation of C4/A1 was used in one child on both recording nights.

The location of the spindle peaks in the power density spectra varies considerably between individuals (Fig. 3-2). Thus, individual spindle peaks and relative spindle power were determined in each subject based on mean all-night power spectra of stage N2 sleep. Using a manual cursor program, the centre frequency of the spindle peak in the power spectrum was marked. To measure the spindle power relative to the background of the power spectrum, a power law function was fit to the spectrum in the range 2-5 Hz and 16-25 Hz, excluding the 5.25-15.75 Hz range (containing theta, alpha and spindle peaks). If more than one peak was present, the peak with the higher frequency was selected (for details see Gottselig, Bassetti, & Achermann, 2002). Individual relative spindle power was determined as power in the range of ± 2 Hz around the individual peak minus background power in the same frequency range (see Figure 3-1 for details). We use the term spindle frequency activity (SFA) or sigma power when referring to the literature where a predefined frequency range, e.g. 12-15 Hz, was used ignoring individual differences.

**Statistical analysis**

To compare sleep stage variables of the two nights paired Wilcoxon tests and Spearman rank correlations were calculated.

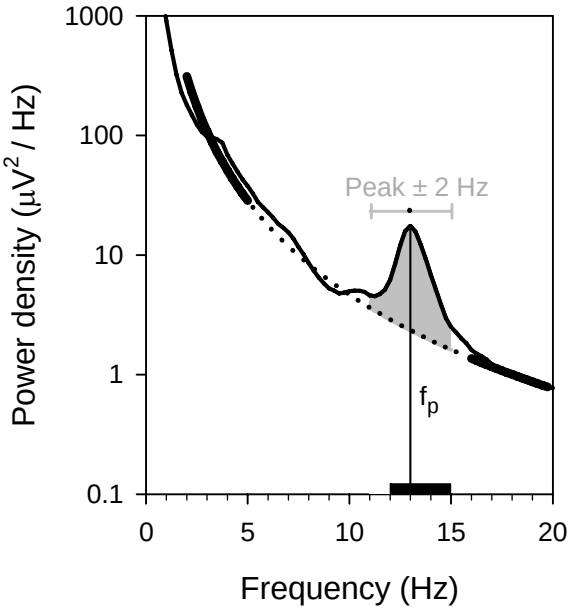
To determine intra-individual stability and inter-individual variability in power density spectra, spectra were used as feature vectors and the Euclidean distance between the vectors was determined. Vectors were log-transformed before calculating distances. Within-subject distances were estimated between the two nights of each subject resulting in fourteen distance values. Between-subject distances were determined between all possible combinations of recordings resulting in 364 values. Within and between subject distances were compared by Mann-Whitney rank sum test. To quantify trait-like aspects in the power density spectra, intraclass correlation coefficients (ICC) were determined for each frequency bin. ICC values were calculated as the between-subjects variance divided by the sum of the between- and within subjects variances (Van Dongen, Baynard, Maislin, & Dinges, 2004).

Spearman rank correlations were calculated to investigate associations between different cognitive abilities and spectral power in each frequency bin (average

spectra of the two nights). Single bins may reach a significant correlation by change, but would not be clustered in a band. Thus, only if at least 6 consecutive frequency bins (a range of 1.5 Hz) showed a significant correlation we considered it as relevant for our interpretation.

Spearman rank correlations were also calculated to investigate associations between different cognitive abilities and individual relative sigma power. To control for potential biases from age effects or time being awake before the sleep recording, two post-hoc multiple linear regression analyses were calculated. One analysis included the predictors age, time being awake before sleep recording and full scale IQ, while the second analysis included the predictors age, time being awake before sleep recording and fluid IQ. Individual relative sigma power was used as criterion variable for both multiple linear regression analyses.

Figure 3-1: Method used to determine the *individual* relative sigma power. Example of a mean all-night power spectrum of N2 sleep (single subject). A power law function (bold and dotted line) was fit to the data in the range of 2-5 and 16-25 Hz, excluding the 5.25-15.75 Hz range (containing theta, alpha and spindle peaks, dotted line). The peak frequency ($f_p$; i.e. average frequency of sleep spindles) was determined using a manual cursor program. Individual relative sigma power: determined as power in the range of ± 2 Hz around the peak minus background power in the same frequency range (grey area). Spindle frequency activity (SFA) or sigma power: power in the 'classical' frequency range of 12-15 Hz (indicated by a black bar on the frequency axis), ignoring individual differences in position of the peak.




## RESULTS

### Cognitive variables

Scores of cognitive variables (Table 3-1) were above population average of the corresponding age group ($p<.05$, one-sample t test), but with a similar standard deviation (SD) ($p>.05$). The distributions were unimodal and did not differ from a normal distribution ($p>.05$; Shapiro-Wilks Test). One child scored as moderately gifted (scores in the range of 130 to 144). Alertness and reaction times in the go/nogo test did not correlate with any of the cognitive and sleep variables (derived from scoring and the sleep EEG).

Table 3-1: Cognitive and attentional variables assessed by WISC IV and KITAP (n=14)

| | mean (M) | standard deviation (SD) | range |
|---|---|---|---|
| IQ | 116.6 | 12.8 | 93 - 137 |
| Fluid IQ | 112.9 | 12.9 | 91 -133 |
| Verbal IQ | 117.6 | 14.7 | 93 – 144 |
| Speed of processing | 116.4 | 12.7 | 100 - 141 |
| Working memory | 116.5 | 12.0 | 84 – 138 |
| Alertness | 57.6 | 8.2 | 40 - 70 |
| Reaction time Go/Nogo | 59.5 | 7.0 | 50 - 71 |

Population norms (age-standardized) for full scale IQ and indices fluid IQ, verbal IQ, speed of processing and working memory are mean (M)=100 and standard deviation (SD)=15.
Population norms (age-standardized) for alertness and go/nogo are M=50, SD=10.

**Sleep variables derived from visual scoring**

Sleep stage distribution, wake after sleep onset (W), sleep latency (SL; defined as the first occurrence of N2), rapid-eye movement (REM) sleep latency (RL; defined as the first occurrence of REM sleep) and sleep efficiency (SE, defined as total sleep time as % of time in bed) did not differ between the two nights (paired Wilcoxon test). However, the total sleep time (TST) was longer for the second night ($Z$=-2.4, $p$<.05, paired Wilcoxon test, Table 3-2). There was no effect of age or time being awake before the recording on any of the sleep variables (F(2,10)=0.3 – 3.8, $p$>.05, multiple linear regression analysis). Daytime sleepiness assessed as sum score of the PDSS was low (7.5; SD = 4.1, a PDSS score of 16 corresponds to the 50$^{th}$ percentile).

To compare both nights in terms of sleep stage distribution, Spearman correlations between the two nights were calculated. All variables related to sleep stage distributions showed significant correlations, with the highest correlation observed for the percentage of NREM sleep. W, SL, RL, TST, and SE did not correlate between the two nights (Table 3-2).

Table 3-2: Sleep variables derived from visual scoring (n=14, two nights per subject)

| | Night 1 | | Night 2 | | Paired Wilcoxon test | Correlations |
|---|---|---|---|---|---|---|
| | MD | range | MD | range | | |
| % stage N1 sleep | 8.3 | 1.7 - 16.0 | 8.3 | 4.5 – 16.5 | n.s. | .75 ** |
| % stage N2 sleep | 40.4 | 34.3 - 61.0 | 46.4 | 36.2 – 53.6 | n.s. | .68 ** |
| % stage N3 sleep | 26.2 | 13.6 – 35.0 | 26.6 | 15.8 – 35.1 | n.s. | .64 * |
| % stage R sleep | 20.8 | 12.6 – 28.8 | 19.8 | 12.9 – 27.8 | n.s. | .57 * |
| % stage N sleep | 70.4 | 62.7 – 79.8 | 72.2 | 61.1 – 79.3 | n.s. | .76 ** |
| Wake after sleep onset (min) | 27.4 | 12.7 – 128.3 | 18.3 | 4.0 – 72.3 | n.s. | n.s. |
| Sleep latency (min) | 23.2 | 0 – 62.0 | 16.0 | 6.7 – 43.7 | n.s. | n.s. |
| R sleep latency (min) | 140.7 | 53.0 – 215.7 | 143.2 | 51.3 – 178.3 | n.s. | n.s. |
| Total sleep time (min) | 442.2 | 388.3 – 502.3 | 477.3 | 385.0 – 521.7 | Z= -2.04 * | n.s. |
| Sleep efficiency (%) | 90.5 | 72.0 – 96.8 | 92.0 | 77.6 – 98.0 | n.s. | n.s. |

Percentages of stage N1, N2, N3, R and N refer to total sleep time; sleep latency is defined as the first occurrence of N2; sleep efficiency is total sleep time as % of time in bed.

stage N sleep refers to stage N2 plus stage N3

MD= median; * p<.05; ** p<.01

Paired Wilcoxon tests are based on between-subjects comparisons (night 1 vs. night 2)

Paired correlations are calculated within-subjects

**Power density spectra**

Total power (0.75 - 20 Hz) of the NREM sleep EEG did not differ between the two nights (Night 1: 2887.89 $\mu V^2$, Night 2: 2503.22 $\mu V^2$; $p$= .78, paired t-test). In

general, the power density spectra were characterized by a large variability between, but a small variability within subjects. Power density spectra of two nights of a given subject largely overlapped (Figure 3-2, upper panels) while considerable differences between subjects were present.

ICC were determined for each frequency bin (Fig. 3-2, lower right panel). Values ranged from .72 to .96, reflecting substantial to almost perfect stability of the spectra of the two nights (Landis & Koch, 1977). Furthermore, using power density spectra as feature vectors, within-subject and between-subject Euclidean distances were calculated and compared (see Methods). Within-subject distances (MD = 1.3; Fig. 3-2, lower left panel) were smaller than between-subject distances (MD = 4.9; $T$= 176, $p$<.001, Mann-Whitney Rank Sum Test) indicating trait-like features in power density spectra of the NREM sleep EEG.

Given the relatively high intra-individual stability in terms of sleep stage distribution and spectral power, mean values of two nights per subject were calculated and used to analyze associations between cognition and sleep.

**Relationship between cognitive abilities, sleep and the sleep EEG**

To explore the relationship between cognitive variables and sleep EEG power density spectra, Spearman rank correlations between cognitive variables and spectral power were calculated for each frequency bin (Figure 3-3; average spectra of the 2 nights; N2 and N3 sleep separately). Several bands of significant correlations between spectral power and cognitive scores were observed, in particular for full scale IQ (10-13.25 Hz; > 15.5 Hz), fluid IQ (> 13 Hz) and working memory (> 16 Hz). These bands were similar for N2 and N3. Verbal IQ and speed of processing did not reveal bands of significant correlations. Only positive correlations in the alpha, sigma and beta range were observed, but not in the delta and theta range. Similar bands of positive correlations were present in REM sleep for full scale IQ, fluid IQ and working memory (data not shown).

Figure 3-2: Upper panels: Power density spectra of N2 sleep of all subjects (two nights per subject, presented in the same colour); left panel: subjects 1-7, right panel: subjects 8-14. Lower left panel: Distribution (box plot) of Euclidean distances (power density spectra used as feature vector) within (14 values) and between subjects (364 values). Boxes represent the lower quartile, median, and upper quartile. Whiskers above and below the box indicate the 90$^{th}$ and 10$^{th}$ percentiles. Outliers are indicated by ●. Lower right panel: Intraclass correlation coefficients (ICC).

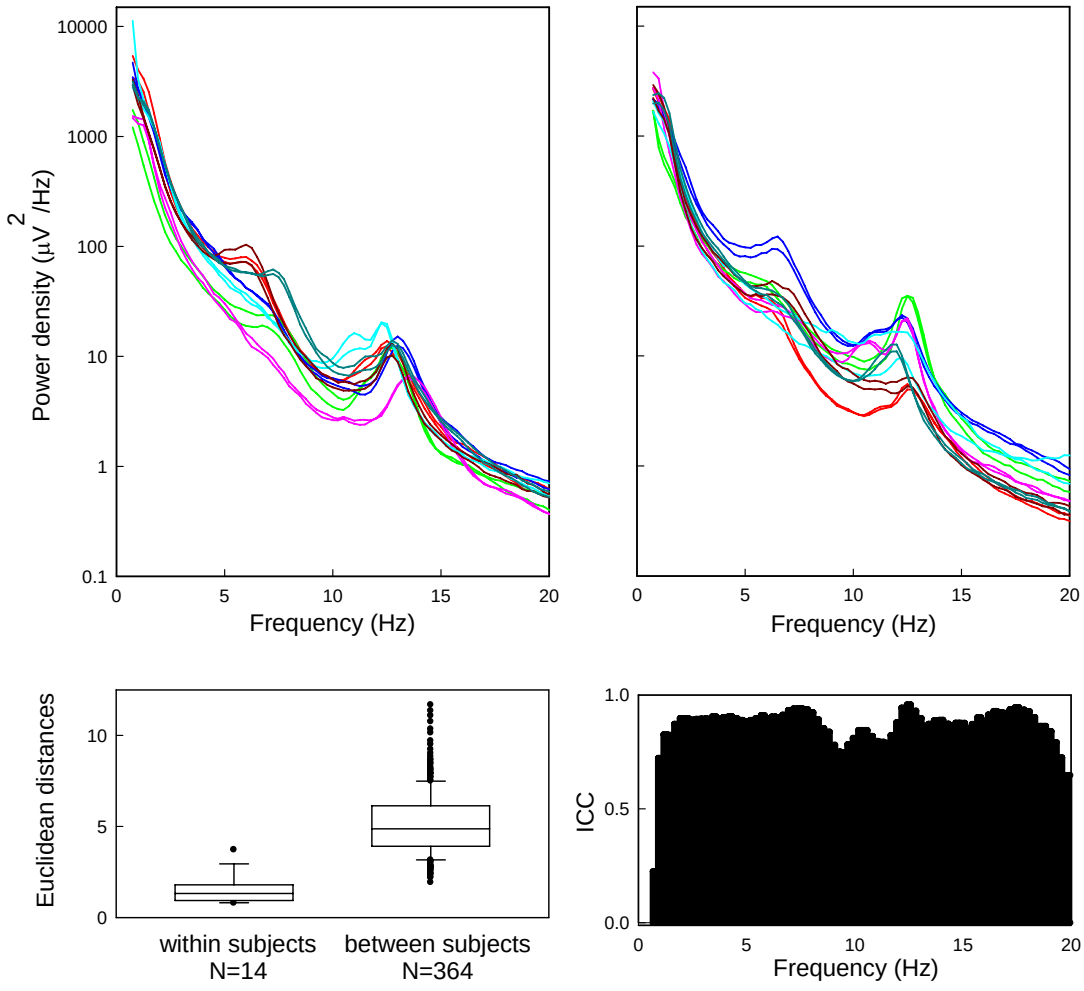
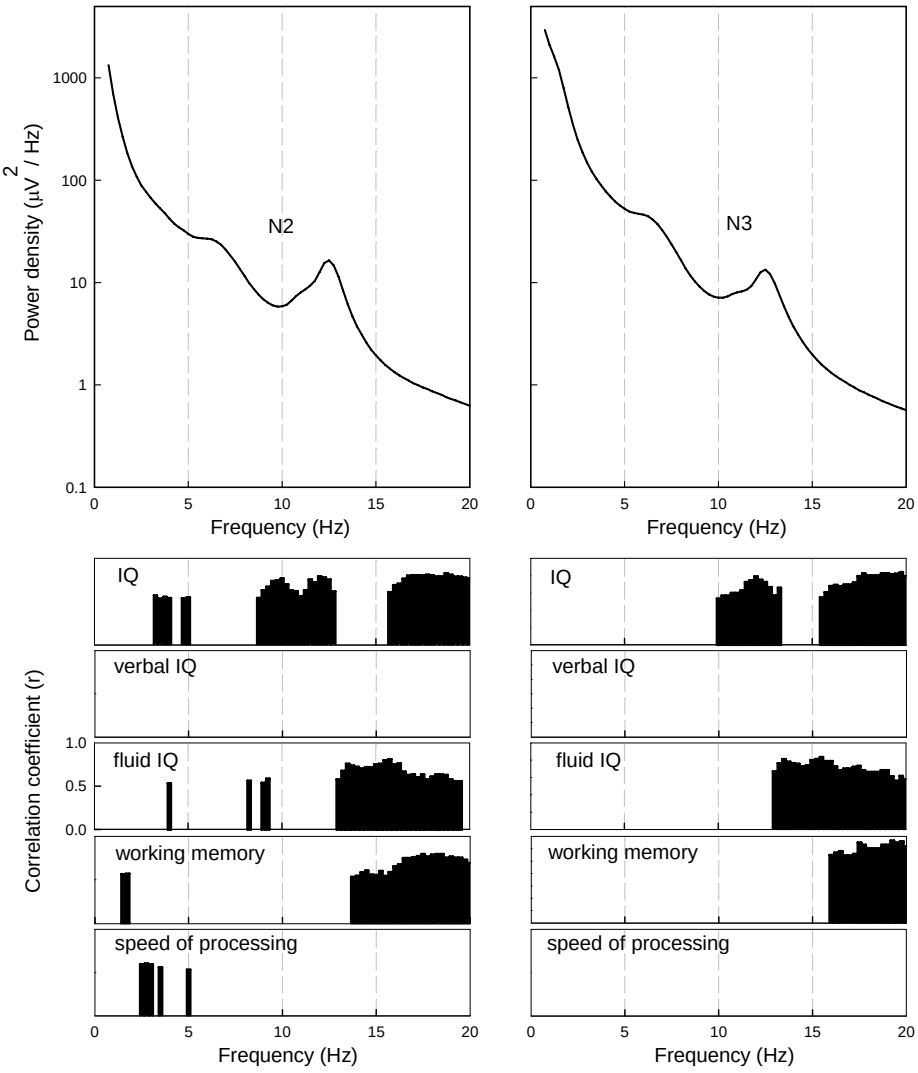


Figure 3-3: Spearman rank correlations between spectral power and cognitive variables. Upper left panel: mean power density spectrum (all nights) of N2 sleep. Upper right panel: mean power density spectrum (all nights) of N3 sleep. Lower panels: Significant correlations for different cognitive variables.




Furthermore, we visually identified individual sleep spindle peaks for each subject (in N2 sleep only). Sleep spindle peak frequency (M= 12.5 Hz, SD= 0.4 Hz) correlated negatively with full scale IQ *(r*=-.56, *p*<.05*)*, that is, the higher the IQ, the lower the sleep spindle peak frequency. Peak frequency did not correlate with any other of the cognitive variables. Correlations were also calculated between individual relative sigma power (power ± 2Hz around peak

relative to the background EEG) and cognitive variables. Individual relative sigma power correlated positively with full scale IQ ($r$=.67, $p$<.01) and fluid IQ ($r$=.65, $p$<.05) accounting for about 45% of the variability in full scale IQ scores and 42% of the variability in fluid IQ scores. Verbal IQ, working memory and speed of processing were not related to individual relative sigma power, and the observed relationship between to individual relative sigma power and intellectual abilities were neither modulated by age nor time being awake before the sleep recording (full scale IQ: $F(3,9)=1.8$, $p>.05$; fluid IQ: $F(3,9)=2.4$, $p>.05$; multiple linear regression analysis).

## DISCUSSION

This study demonstrated for the first time a high within-subject stability of the sleep EEG in 9 to 12 year old children. Sleep stage distribution and spectral power was highly correlated between two nights of the same child, with a large intraindividual similarity and interindividual variability. We found a similar characteristic phenotype of the sleep EEG as reported in the adult literature (Ambrosius et al., 2008; Buckelmüller, Landolt, Stassen, & Achermann, 2006; De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005; De Gennaro et al., 2008; Finelli, Achermann, & Borbély, 2001; Linkowski, 1999). Although the analysis was based on a small population and included only two nights per subject, the trait-aspect of the sleep EEG was consistent and corroborated earlier findings in adults. Thus, we are confident that the results reflect a general disposition and not an experimental effect evoked by the sleep laboratory environment. As mentioned earlier (Ambrosius et al., 2008; Finelli, Achermann, & Borbély, 2001), features of the sleep EEG may represent the functional aspects of the underlying brain anatomy or individual characteristics of brain morphology. Based on these findings we conclude that trait-like aspects, i.e., high within-subject stability in the sleep EEG are present in children.

Apart from the trait-like aspects of children's sleep, we found a relationship between the sleep EEG and intellectual ability in healthy children, which was not reported before. Overall, there were positive associations between spectral power in specific frequency ranges and cognitive scores with significant correlations clustered in the alpha, sigma and beta range, but not for frequencies in the delta and theta range. Thus, the higher the power in specific frequency bands, the higher the performance of specific cognitive variables. In adults, it

has previously been observed that sigma power is related to intelligence scores (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2008). However, the association between alpha and beta power with cognitive variables has never reported before. Given the lack of data in adults, we cannot state whether our results are unique to children or whether the relationship between alpha or beta power and cognitive variables has simply not been considered in previous studies of adults.

Interestingly, we found a dissociation between different components of intellectual ability in their relationship with physiological correlates - the positive associations between spectral power and cognitive variables were primarily restricted to full scale IQ, fluid IQ and working memory, but not observed for verbal IQ and speed of processing. The dissociation between full scale IQ and fluid IQ being related and verbal IQ being unrelated to spectral power of the sleep EEG has been observed before and, thus, our results extend and corroborate earlier findings in adults (Fogel, Nader, Cote, & Smith, 2007).

Fluid IQ, the non-verbal dimension of intellectual capacity (e.g., the ability to solve new problems independent of acquired knowledge) was originally defined as "the influence of biological factors on intelligence" (Horn & Cattell, 1966). Based on this concept, fluid IQ may be understood as a component of intellectual ability which is closely related to neuronal processing; or in other words, fluid IQ may reflect the "hardware" of human intelligence. Working memory has been defined as "the ability to hold in mind information in the face of potentially interfering distraction…" (Jarrold & Towse, 2006), which is a sub domain of executive functions. Genetic influences on executive functions have been estimated to reach approximately 50% (Rose, 1995). Moreover, it has been reported that working memory and fluid IQ partially rely on a common process namely attentional control (Gray, Chabris, & Braver, 2003; Patrick C. Kyllonen & Christal, 1990). Therefore these processes share a certain amount of variability with correlation coefficients ranging from .36 (Gray, Chabris, & Braver, 2003) to .7 (Süss, Oberauer, Wittmann, Wilhelm, & Schulze, 2002). Imaging data is pointing towards the same direction: a considerably high overlap of neural circuitries involved in both working memory and fluid IQ with networks primarily located in lateral prefrontal and the parietal cortex (Gray, Chabris, & Braver, 2003; Kane & Engle, 2002). In this sense, physiological correlates for those

components of intellectual capacity that are more nature as opposed to nurture driven seems plausible.

Despite the large body of evidence on the relationship between waking EEG parameters and cognitive ability (Klimesch, 1999; Neubauer, Fink, & Grabner, 2006; Thatcher, North, & Biver, 2005), surprisingly little research has been performed to elucidate the association between cognitive ability and the sleeping brain. Up to now, the focus has been on the relationship between cognitive ability and SFA with studies reporting positive associations (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2008) – the higher the SFA, the higher the cognitive ability. This relationship has however, not been shown for children. Our data, which corroborate these earlier findings in adults, allows for extension – the relationship between cognitive ability and SFA is already present in childhood. Studies in the context of sleep and learning also highlighted the importance of sleep spindles or SFA at the state-level (Abad & Guilleminault, 2005; Clemens, Fabo, & Halasz, 2005; Gais, Molle, Helms, & Born, 2002; Schmidt et al., 2006).

Sleep spindle oscillations have been speculated to play a dominant role in gating plastic changes during sleep and may represent a candidate physiological mechanism for memory consolidation (Sejnowski & Destexhe, 2000). Given this often cited and appealing hypothesis for the functional role of sleep spindles, it is not surprising that the main focus of research for a physiological correlate of intelligence during sleep has been on sleep spindles or SFA. Our data shows, however, a more nuanced picture: We found a negative association between spindle peak frequency (i.e. average frequency of spindles) and full scale IQ. Thus, the lower the sleep spindle peak frequency in the power spectra, the higher the full scale IQ scores. Earlier studies have not reported associations between spindle peak frequency and cognitive ability. The spindle peak is subjected to substantial developmental changes, and may therefore be used as a marker of brain maturation. It has been reported that the peak frequency of the sleep spindles increases with age. For example, older children show higher spindle peak frequencies (Shinomiya, Nagata, Takahashi, & Masumura, 1999; Tarokh & Carskadon, 2010). If we assume that those children with higher IQ scores are developmentally advanced, our findings seem contradictory at a first glance, because we would expect a positive relationship between spindle peak and IQ scores. However, data on the age-related increase of the spindle peak

frequency is based on cross-sectional studies, and must therefore be interpreted with caution. Our data resemble a snap shot in a specific age group. Moreover, it has been reported that adolescent girls may even have faster spindles than adults (Nader, Smith, Muir, & Scharfe, 2003). Finally, it is not clear, how chronological age, brain maturation and cognitive development co-evolve and interact. Our data are, however, in accordance with previous studies in adults (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2008). We found a positive relationship between full scale IQ scores, fluid IQ scores and individual relative sigma power.

To date, there is only one other study on the relationship between the sleep and intelligence in children, but the reported effects were on IQ scores related to the percentage of stage 2 sleep rather than a direct measure of EEG activity (Busby & Pivik, 1983). From a clinical point of view, several sleep EEG variables have been proposed to reflect the integrity of the central nervous system. Specifically, it has consistently been reported that alterations in SFA, number of sleep spindles or percentage stage 2, are affected by pathological changes of the nervous system (e.g. in neurodegenerative disorders such as in Alzheimers' and Creuzfeld Jacobs' disease (Petit, Gagnon, Fantini, Ferini-Strambi, & Montplaisir, 2004)), by ischemic events (Gottselig, Bassetti, & Achermann, 2002), and in psychiatric diseases such as schizophrenia (Ferrarelli et al., 2007). In addition, children with mental retardation showed either large amounts of SFA or virtually none (Shibagaki, Kiyono, & Watanabe, 1982). In light of the previously reported positive association between intelligence and SFA in healthy subjects, an increased SFA in children with mental retardation (Bixler & Rhodes, 1968; Gibbs & Gibbs, 1962) appears counter-intuitive on the first glance. However, Fogel et al. (2010) have postulated that the relationship between intelligence and SFA may be U-shaped or curvilinear. Thus, our data would indeed conform with the predictions of this hypothesis – a positive association between IQ scores and SFA in a population with average to superior intellectual ability.

One limitation of the present study was the relatively small sample whose IQ scores were higher than average. Thus, it may be argued that the reported associations between variables of the sleep EEG and intellectual ability that we found may be a property of this specific population. However, based on the fact that IQ scores covered a reasonably broad range of variability (SD similar as for the population; Tab. 3-1) and that children were healthy and not sleep deprived

(as revealed by screening interviews and validated questionnaires), we believe that our results are generalizable up to certain degree. However, the findings are only of a correlational nature and thus have to be interpreted with caution. Finally, the sample size was too small to examine age or gender effects. Moreover, daytime activities such as sports or music were neither controlled nor systematically manipulated. Thus, we cannot rule out the possibility that state-dependent sources of variance may have contributed to the inter-individual differences in the sleep EEG. Nevertheless, stable night to night power density spectra were observed within subjects (Fig. 3-2) indicative of a trait aspect. Future studies are needed to replicate the reported associations and to further differentiate between state-and trait-related sources of variance. For example, it would be promising to investigate a larger group of children with a broad age range, to apply systematic sleep manipulations and to perform a longitudinal study. It also may be worthwhile to follow the approach of Schabus (2008) and differentiate between trait-related hardwired individual differences in intelligence as opposed to learning-induced short-term changes in their association with SFA.

In sum, we demonstrate that high within-subject stability in the sleep EEG (trait-like aspects) is already present in childhood. Moreover, we found that inter-individual differences of the sleep EEG were related to intellectual ability – full scale IQ, fluid IQ and working memory. The sleep spindle frequency peak as well as sigma power was particularly associated to full scale and fluid IQ. Many empirical observations have related differences in IQ scores to variations in brain structure and function (for review see Jung & Haier, 2007). The neuronal network properties underlying these intellectual differences are supposedly hardwired and thus should be identical regardless of the actual state – be it for the waking or the sleeping brain. Whereas studies performed during wakefulness may be biased by many external influences such as attention, motivation or temporal fluctuations in current mood, studies performed on the sleeping brain may be less affected by these potential sources of interference. Eventually, it may be speculated that the human sleep EEG and intellectual ability are epiphenomena of the same underlying processes, representing two facets of the same individual trait.

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## Addendum: Intellectual ability and dynamics of slow-wave activity

Slow-wave activity (SWA, spectral power in the frequency range between 0.75-4.5Hz) during NREM sleep is homeostatically regulated and has been interpreted to reflect sleep pressure accumulated during wakefulness (Borbély, 1982). Recently a comprehensive hypothesis regarding the function of SWA has been formulated, the synaptic homeostasis hypothesis (Tononi & Cirelli, 2003, 2006). It postulates that SWA represents a process which reduces or depresses synaptic strength following daytime stimulation, thereby preventing over potentiation of the whole network.

In the developmental context, it is known that certain aspects of sleep homeostasis change during childhood. For example, absolute SWA is higher for younger children compared to adolescents (Gaudreau, Carrier, & Montplaisir, 2001; Jenni & Carskadon, 2004) and SWA continuously shifts from posterior to anterior regions during development (Kurth, Ringli et al., 2010). This developmental time course of SWA may parallel maturational changes in brain morphology, with brain regions that are associated with basic sensory or motor functions maturing first, followed by those involved in more complex behavior and cognitive functions (for review see Casey, Tottenham, Liston, & Durston, 2005). In particular, the maturation of the frontal lobe is known to follow a specific time course characterized by a preadolescent increase followed by a postadolescent decrease in cortical grey matter (Shaw et al., 2006; Sowell et al., 2004). Both, the time course of synaptic density (Giedd et al., 1999; Huttenlocher, 1979) and SWA (Campbell & Feinberg, 2009; Feinberg, 1982) follow an inverted U-shaped time course. This striking similarity has led to the assumption that SWA reflects cortical maturation and plasticity during development (Buchmann et al., 2010; Campbell & Feinberg, 2009; Feinberg & Campbell, 2010; Kurth, Ringli et al., 2010).

Given that test scores of IQ tests are based on age-standardized norms, without taking individual developmental dynamics in brain maturation into account, one may assume that those children that are advanced in terms of neural maturation, are also characterized by a more mature cognitive profile (i.e., higher IQ scores).

Finally, if advanced neural maturation results in more mature sleep EEG characteristics (in particular those variables related to SWA) and more mature cognitive profile, a relationship between SWA and intelligence scores seemed highly plausible.
Besides, on the state-level, a growing body of research relates SWA to performance enhancement following different learning tasks (Gais & Born, 2004; Huber, Ghilardi, Massimini, & Tononi, 2004; Walker & Stickgold, 2004). Therefore, we expected specific components of SWA (e.g., absolute SWA for the whole night or within the first sleep cycle, decay rate of SWA reflecting the homeostatic process) being related to cognitive ability.

Fourteen healthy children (mean age 10.5±1.0 years; 8 male) have been analyzed (identical population as for study III). After the assessment of intelligence (full scale IQ and separate indices verbal IQ, fluid IQ, working memory, speed of processing), all-night polysomnography was performed (two nights per subjects, usually separated by one week). One child had to be excluded from the analysis due to a failure during the recording session (recording started too late). As determined by actigraphy and questionnaires, children were not sleep deprived prior to the sleep recordings. Spectral analysis was performed on artefact-free NREM epochs (C3/A2 derivation). Sleep cycles were determined according to standard criteria (Feinberg & Floyd, 1979; Rechtschaffen & Kales, 1968) and adapted to account for frequently occurring "skipped" REM sleep after the first NREM sleep episode (see Jenni, Achermann, & Carskadon, 2005; Kurth, Jenni et al., 2010). Mean SWA per NREM sleep episode was calculated. To calculate the decay time constant, the two nights of a given subject were pooled (individual means of SWA per NREM sleep episode at episode midpoints). For details on the study population, experimental procedure and descriptive statistics on the cognitive and sleep variables see study III.

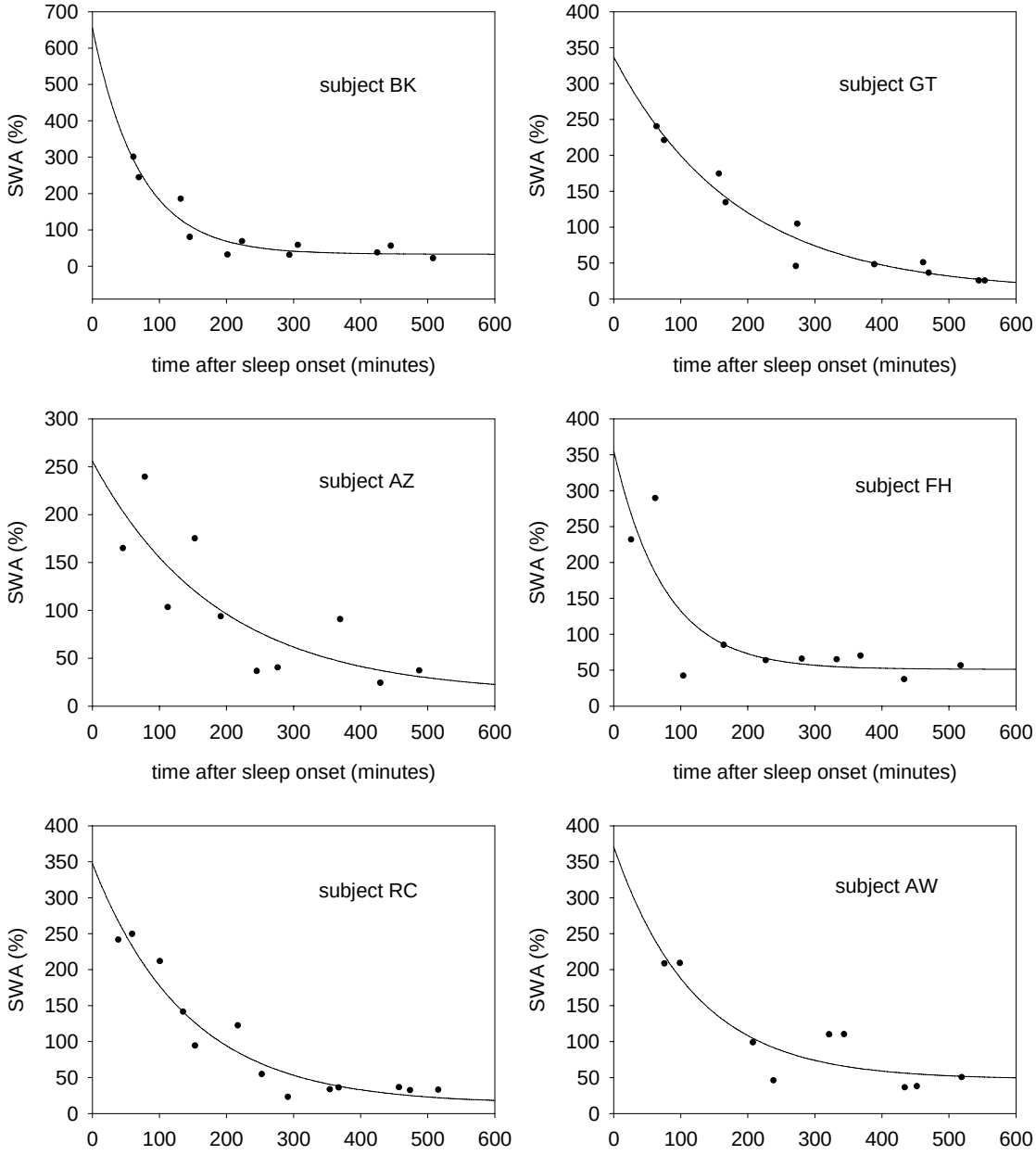
Table 3-3: Descriptive statistics of sleep cycles, initial absolute and relative value of SWA in the first cycle and parameter estimates of the exponential function (decay time constant and lower asymptote).
2 nights per subject (N=13), 26 nights in total.

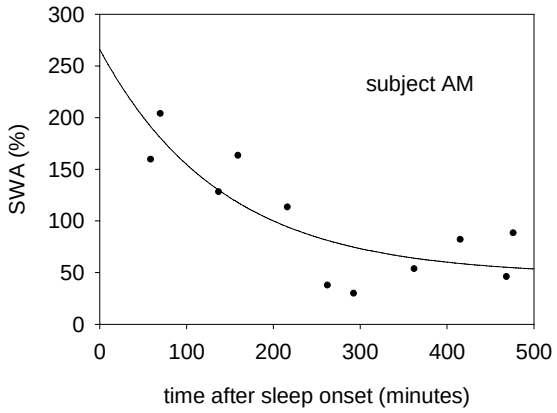
| | Mean | SD | Min | Max |
|---|---|---|---|---|
| Number of completed sleep cycles (incl. "skipped" REM) | 4.8 | 0.9 | 3 | 7 |
| Mean sleep cycle length (min) | 89.0 | 13.3 | 75.0 | 125.5 |
| Mean value of SWA in the first NREM sleep episode ($\mu V^2$) | 4387.5 | 1776.4 | 1771.3 | 9024.3 |
| Relative SWA (initial SWA relative to average nocturnal value during NREM sleep) (%) | 217.9 | 45.7 | 147.7 | 340.3 |
| Decay time constant ($\tau$) (min) | 133.0 | 61.9 | 23.8 | 249.7 |
| Lower asymptote of the exponential decay function (%) | 28.3 | 33.5 | -68.8 | 62.9 |

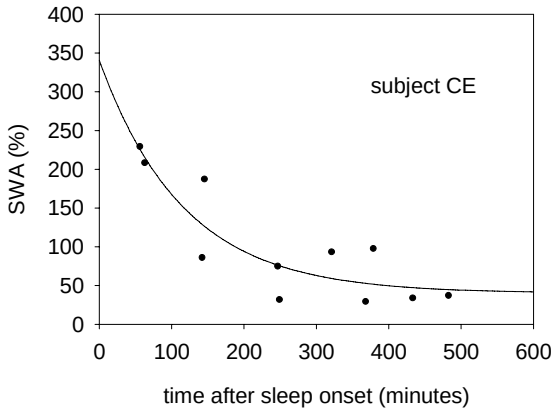
"skipped" REM: no REM sleep after first NREM sleep episode (9 out of 13 children)
SD= standard deviation; Min= minimum; Max= maximum

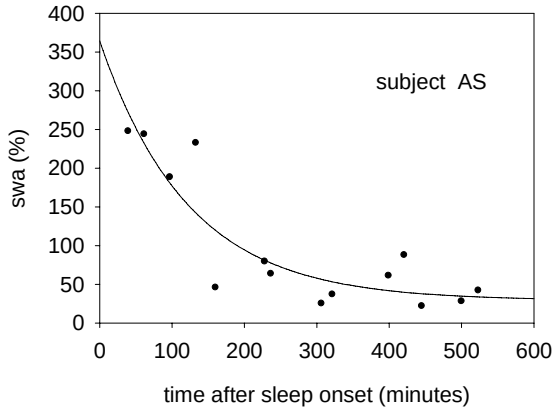
Partial correlations (controlled for age and time being awake before the sleep EEG recordings) were computed among the different sleep variables related to SWA (*number and mean sleep cycle length*, *mean value of SWA in the first NREM sleep episode*, *decay time constant*, *lower asymptote*, see table 2) and the cognitive variables (*full scale IQ*, *verbal IQ*, *fluid IQ*, *working memory* and *speed of processing*) for the total study population (N=13). There was no correlation ($p<.05$) between any of the cognitive variables and those related to SWA (*number and mean sleep cycle length*, *initial value of SWA*, *decay time constant*, *lower asymptote*).

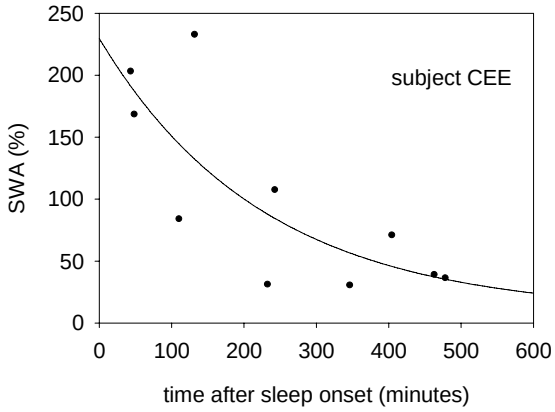
Figure 3-4: Dynamics of SWA across consecutive NREM sleep episodes. SWA is expressed as percentage of the average nocturnal value during NREM sleep. Individual means per NREM sleep episode are plotted at episode midpoint times relative to sleep onset (2 nights per subject, pooled). Lines represent exponential functions, which were fit to the data using the following equation:
SWA (t) = $SWA_0 * e^{-t/\tau} + SWA_\infty$ ($SWA_\infty$: asymptote; $\tau$: time constant; $SWA_0$: initial value minus asymptote). Individual subjects (N=13). All individual exponential fits converged.

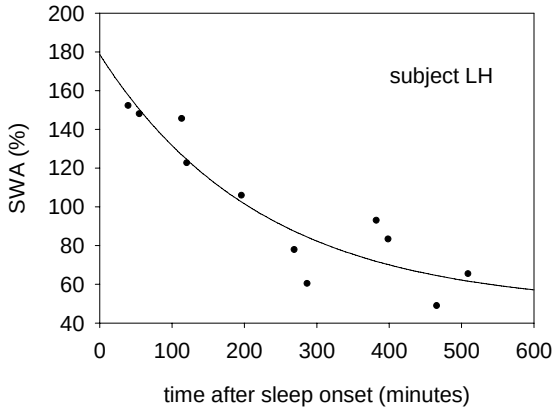


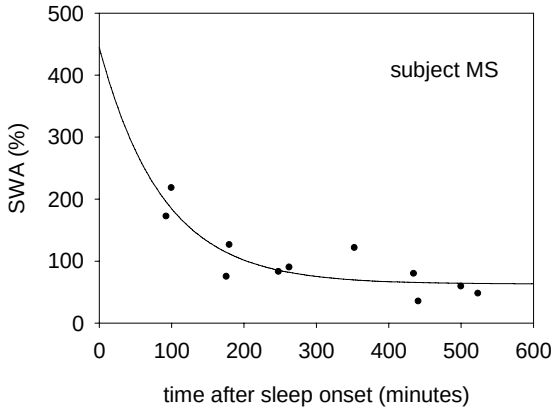

subject AM
SWA (%)
time after sleep onset (minutes)


subject CE
SWA (%)
time after sleep onset (minutes)


subject AS
swa (%)
time after sleep onset (minutes)


subject CEE
SWA (%)
time after sleep onset (minutes)


subject LH
SWA (%)
time after sleep onset (minutes)


subject MS
SWA (%)
time after sleep onset (minutes)

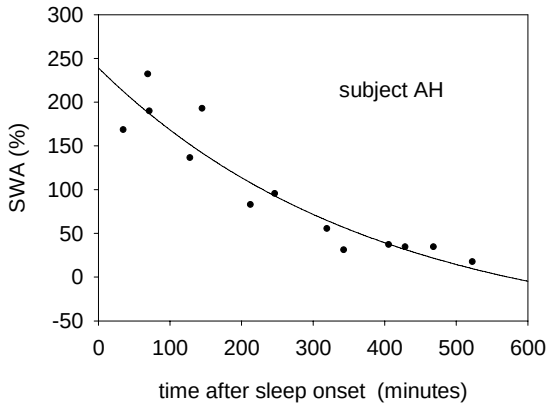
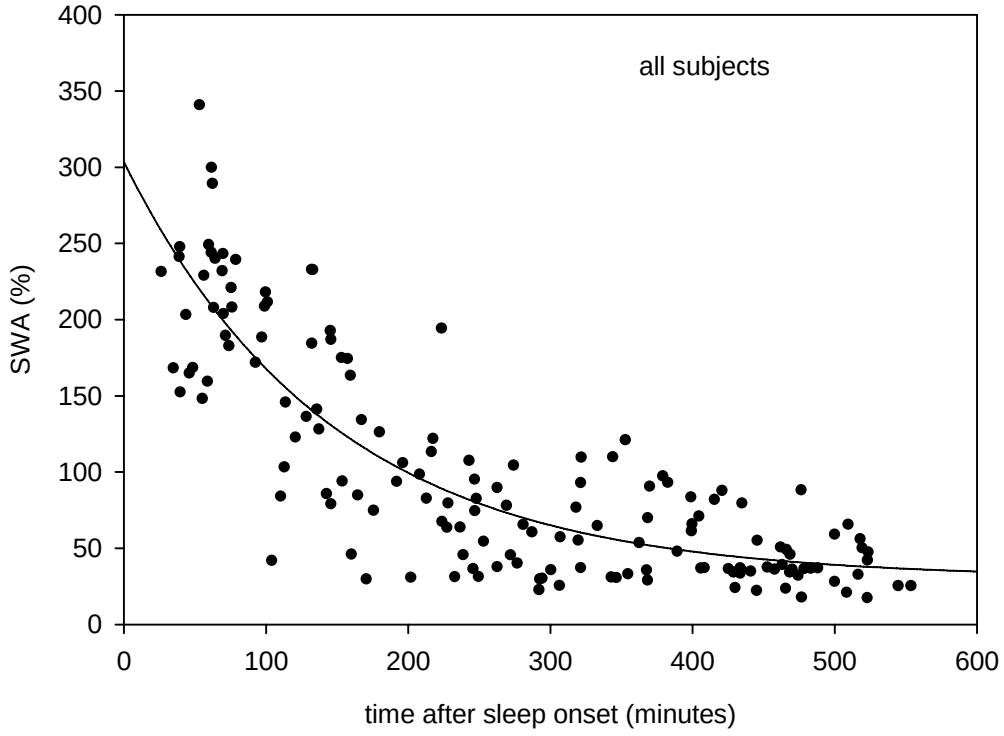

subject AH
SWA (%)
time after sleep onset (minutes)

Figure 3-5: Dynamics of SWA across the sleep episodes. SWA is expressed as percentage of the average nocturnal value during NREM sleep. Individual means per NREM sleep episode are plotted at episode midpoint times relative to sleep onset (2 nights per subject (N=13); 26 nights). Line represents exponential function ($r^2$=0.73), which was fit to the data using the following equation:
SWA (t) = $SWA_0$ * $e^{-t/\tau}$ + $SWA_\infty$ ($SWA_\infty$: asymptote; τ: time constant; $SWA_0$: initial value minus asymptote). Exponential fit converged.
Mean exponential function for of all subjects (2 nights per subject, N=26 nights):
SWA (t) = 273.2%*$e^{-t/145.6}$ + 30.3%




Thus, contrary to our expectations, there was no relationship between cognitive variables and those related to SWA (*number and mean sleep cycle length*, *mean value of SWA in the first NREM sleep episode*, *decay time constant*, *lower asymptote*) in our study population.
It may, however, be that potential associations between variables related to SWA and intellectual ability have been masked due to the following reasons: First, there was no adaptation night, although it is well known that certain variables of

the sleep EEG are affected by the so-called first night effect (Agnew, Webb, & Williams, 1966). For example total sleep time and sleep efficiency are lower and there is more intermittent wake time for first nights spend in the sleep laboratory (Le Bon et al., 2001). Second, the experimental conditions varied between recording sessions and the subjects - the start of the sleep recording varied up to one and a half hours. Third, the heterogeneity between subjects and nights in terms of "skipped" REM sleep episodes, sleep latency and wake after sleep onset was considerably large. Nine out of 13 children had no REM sleep between the first and the second sleep cycle ("skipped" REM sleep). Although we manually subdivided the first NREM sleep episode according to the criteria by Jenni (2004) and Kurth (2010), this procedure may have influenced the results. Moreover, six out of 13 children had at least one night with long waking periods (>45 min). These long waking periods during the night are especially problematic in the sense that it may have caused a rebuilding of homeostatic sleep pressure and thus biased the common exponential decline of SWA across NREM sleep episodes.

Apart from these potential biases that originate from the experimental weakness of the current study, it may also be that SWA is completely uneligible as a marker of intellectual ability. SWA which has been suggested as a process which reduces or depresses synaptic strength following daytime stimulation is in fact closely related to immediate and precisely circumscribed changes, induced by direct stimulation (e.g., by transcranial magnet stimulation (TMS)) or learning of specific tasks that involve narrowly defined local brain areas. The synaptic homeostasis hypothesis (Tononi & Cirelli, 2003, 2006) postulates that SWA represents a general process which reduces or depresses synaptic strength following daytime activity, thereby preventing over-potentiation of the whole network. Although there is extensive empirical support for this hypothesis in general and in particular for concrete and precisely defined learning tasks such as the acquisition of a certain motor sequence, it is difficult to imagine that the mechanism of downscaling sufficiently explains more complex abilities and behavior on the trait-level, such as intellectual ability. Complex intellectual abilities (i.e. intelligence) rely on multimodal input and the simultaneous integration of newly acquired into already established networks. Motivational and attentional resources as well as behavioral contingencies modulate the acquisition of complex intellectual abilities. Thus, in the context of the synaptic

homeostasis hypothesis, complex behavioral phenomena on the trait-level (e.g., intelligence) may raise the following questions: How are the individual synapses for downscaling identified in complex real-life situations with parallel input from multiple sources? To what extend are the synapses downscaled? Which synapse of an activated network is downscaled to what extend in a given situation?

Study IV

## Sleep EEG topography and intellectual ability

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In preparation

**ABSTRACT**

To investigate the relationship between the topography of the children's sleep EEG (high-density EEG) and their intellectual ability, correlations between band power and IQ variables were computed for 109 EEG derivations. Spectral power in the alpha, sigma and beta range was correlated with scores of full scale IQ, fluid IQ and working memory (14 subjects, mean age 10.5±1.0 years; 6 girls). The previously reported global relationship (C3/A2 derivation) between spectral band power and intellectual ability could further be refined – particular spatial patterns over central and parietal areas with positive correlations were found. Thus neurobiological correlates of intelligence during sleep may show regional pattern.

## INTRODUCTION

Intelligence is a frequently used psychological construct and – although there are numerous definitions – considered an umbrella term for adaptive behavior, and the ability to reason or solve problems (Gottfredson, 1997). In the past decades, several studies and reviews have articulated that intelligence also involves specific neurobiological correlates of both structural and functional nature (for review see Deary & Caryl, 1997; Jung & Haier, 2007; Luders, Narr, Thompson, & Toga, 2009; Neubauer & Fink, 2009). Early anthropometric investigations claimed that total grey matter volume reflects the structural substrate of intelligence (Galton, 1869). As functional correlates, the glucose metabolism rate (GMR) and measures derived from electroencephalography (EEG) have, among others, been related to intelligence with predominantly negative correlation coefficients for the GMR (see Neubauer & Fink, 2009) and positive correlations ranging from approximately .4 to .6 for EEG-based variables (see e.g., Gasser, Von Lucadou-Muller, Verleger, & Bacher, 1983; Thatcher, North, & Biver, 2005). However, most studies not only reported global structural or functional correlates of intelligence, but also tried to specify associations between intelligence and neurobiology at the local anatomical level. For example, Jung and Haier (2007) summarized a multitude of studies that are based on voxel-based morphometry and finally formulated the *parieto-frontal integration theory* (P-FIT). The P-FIT implies that networks of grey matter volumes in specific brain areas but also interactions dependent on the connecting fiber tracts are the biological substrates of intelligence (Jung & Haier, 2007). Likewise, applying different cognitive tasks while simultaneously measuring subjects' GMR, Duncan and colleagues (2000) emphasized that general intelligence derives from selective recruitment of distinct lateral frontal areas, rather than from the global activity level. Thus, the focus of scientific interest shifted from global to local correlates of intelligence.

Despite the large body of historical as well as recent literature on the neurobiological correlates of intelligence during wakefulness, surprisingly little research has been performed to examine these neurobiological correlates of intelligence during sleep. Given that the neuronal network properties underlying individual differences in intellectual ability are supposedly hardwired, an association between intelligence and neurobiological correlates seems highly plausible, regardless of the actual behavioral state – wakefulness or sleep. Up to

now, only a few studies in adults have attempted to identify neurobiological correlates of intelligence during sleep (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2008). However, these studies exclusively focused on sleep spindles or spindle frequency activity (SFA or sigma power, i.e. spectral power in the 12-15 Hz range) in association with intelligence quotient (IQ) scores without reporting associations between IQ scores and EEG power in any other frequency range. Besides, the main focus of analysis has been on global correlates for intelligence during sleep. To our knowledge, only a single study investigated topographical aspects of the relationship between IQ scores and physiological variables of sleep: Bodizs and colleagues (2005) reported that fast spindle density and grouping of fast spindles explained about 70% of variability in IQ scores, but only for the left frontopolar (derivation Fp1, right mastoid reference) and right frontal (derivations Fp2 and F4, left mastoid reference) derivations. Another exploratory study (Fogel, Nader, Cote, & Smith, 2007) which also examined the topography of the relationship between IQ scores and sigma power reported a positive correlation (r=.65) between performance IQ and high sigma power (at Pz derivation only), but included only four midline derivations and thus did not allow for a detailed topographical interpretation of the effects.

We recently investigated the relationship between intelligence and variables of sleep at a global level in children aged 9.1 to 12.5 years old (Geiger et al., 2011). Positive associations between intelligence (full scale IQ, fluid IQ and working memory) and spectral power of the sleep EEG (derivation C3/A2) in the alpha, sigma and beta frequency ranges were found. Based on these previous results, the aim of the present analysis was to explore the relationship between intelligence and spectral power at the topographical level.

## METHODS

### Participants and procedure

A dataset of a previous study (Geiger et al., 2011) was further analyzed. Fourteen right-handed healthy children between 9.1 to 12.5 years of age (8 male, 6 female, mean age 10.5 years, 12 pre-pubertal and 2 mid-pubertal children) participated in the study. Exclusion criteria were chronic diseases, neurological or psychiatric diagnoses (e.g., attention deficit hyperactivity disorder), sleep disorders or drug treatments. The study was approved by the

cantonal ethical committee and was performed according to the Declaration of Helsinki. All families received a detailed study description and provided written informed consent.

The children were assessed with the WISC IV (German version) intelligence test (Petermann & Petermann, 2007) yielding separate indices for fluid intelligence, verbal intelligence, speed of processing and working memory as well as a full scale intelligence quotient (IQ) score. WISC IV scores are standard scores based on age-referenced normative data (see Geiger et al. for details 2011). Only children who had not performed any kind of intelligence testing during the last two years prior to participation in the study were included.

One week prior to the sleep recordings, parents were instructed to maintain childrens' habitual sleep-wake schedules, and to keep a sleep diary with detailed information about bed and wake-up times, caffeine consumption and medication. Compliance with instructions (regular sleep-wake schedules) was verified with actigraphs. Daytime sleepiness was assessed by the Pediatric Daytime Sleepiness Score (PDSS, Drake et al., 2003). All children participated in two recording sessions separated by one or two weeks.

**Sleep recordings, data analysis and processing**

All-night polysomnography was recorded by a high-density EEG system (128 electrodes net, Electrical Geodesic, Inc., for electrode net out layout including positions of the 10-20 system see Supplementary Figure S3 in (Kurth, Ringli et al., 2010)), starting between 9 p.m. and 10.30 p.m. (habitual bed-time of the subjects) and lasting between 8 and 10 hours. Furthermore, the submental electromyogram (EMG) and the electrooculogram (EOG, 2 bipolar derivations) were recorded. EOG electrodes were placed approx. 1 cm below and above the outer canthus. Data were sampled at 500 Hz (0.01 to 200 Hz) referenced to the vertex (Cz).

Sleep stages were visually scored in 20-s epochs based on ASSM standard criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Spectral analysis was performed for 109 channels (excluding the channels below the ears) and average referenced. Data were band-pass filtered (0.5 to 50 Hz) and down-sampled to 128 Hz. EEG power density spectra were calculated for consecutive 20-s epochs (FFT, Hanning window, averages of five 4-s epochs; frequency resolution 0.25 Hz) and matched with the corresponding sleep stages. Artifacts were excluded on

a 20-s basis by visual inspection and semi automatically. Average spectra of NREM sleep (N2 plus N3) were calculated for the minimum common length (6.41 h) of sleep.

Since the two nights of a given child were highly correlated in terms of sleep stage distribution and spectral power, with a large intra-individual similarity and inter-individual variability, mean spectra of two nights per subject were calculated and used for further analysis (for rationale, results and discussion of the reliability of trait-like characteristics of the children's sleep EEG see Geiger et al., 2011).

### Focus of statistical analysis

To investigate associations between intellectual abilities and topographical aspects of spectral power during NREM sleep, Spearman rank correlations were calculated for all 109 derivations, excluding those affected by artefacts (on average, 2 ±2 channels per subject). Based on our previous work (Geiger et al., 2011), however, the analyses were restricted in two aspects: First, only those intellectual variables that showed relationship with global sleep EEG power in NREM sleep (derivation C3/A2) were included in the analysis, namely full scale IQ, fluid IQ and working memory. Second, only those frequency bands that indicated a relationship with cognitive variables, were analysed, namely 10-13.25 Hz and 15.5-20 Hz (full scale IQ), 13-20 Hz (fluid IQ) and 16-20 Hz (working memory), see Figure 4-1.

Maps of spectral band power and of the correlations were plotted with the function 'topoplot' of EEGLAB (Delorme & Makeig, 2004).

## RESULTS

### Cognitive variables

Mean full scale IQ score was 116.6 (±12.8), fluid IQ score was 112.9 (±12.9) and working memory score was 116.5 (±12.0).

### Sleep variables derived from visual scoring (mean nights of two nights per subject)

Mean total sleep time was 457.7 ± 28.3 min, consisting of 70.6 ± 4.7% NREM sleep (stage N2 plus stage N3). Mean sleep efficiency (percentage of total sleep time of time in bed) was 91 ± 4.7%, mean sleep latency (the interval between

lights off and the first occurrence of stage N2) was 23.2 ± 11.7 min and mean REM sleep latency (sleep onset to first occurrence of REM sleep) was 131.9 ± 33.3 min.

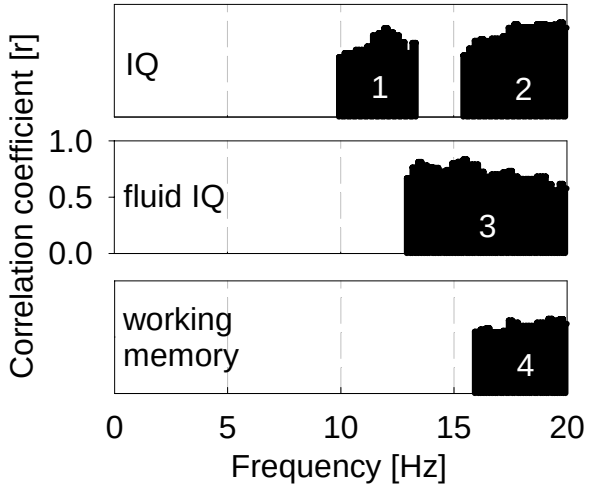
**Relationship between cognitive variables and sleep variables derived from visual scoring**

Scores of working memory correlated with percentage of NREM sleep ($r$=.60, $p$<.05, Spearman rank correlations) and REM sleep (REM sleep=-.56, $p$<.05, Spearman rank correlations).

**Relationship between cognitive variables and the sleep EEG (global analysis)**

Several bands of significant correlations between spectral power during NREM sleep (derivation C3/A2) and cognitive scores were observed, in particular for full scale IQ (10-13.25 Hz; 15.5-20 Hz), fluid IQ (13-20 Hz) and working memory (16-20 Hz). Only positive correlations were found, in particular in the alpha, sigma and beta range, whereas correlations in the delta and theta range did not reach significance (Figure 4-1).

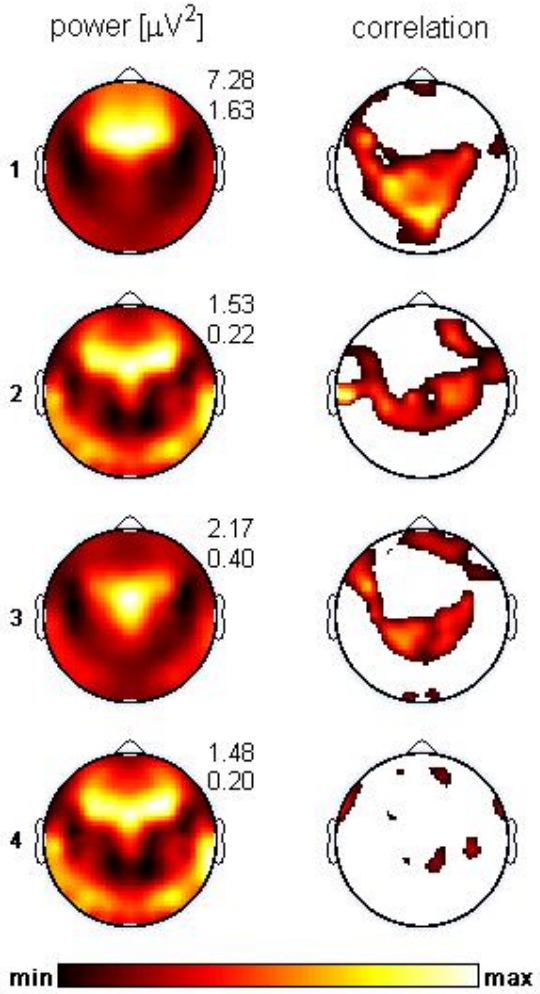
Figure 4-1: Frequency ranges showing significant correlations between spectral power in NREM sleep (stages N2 and N3; derivation C3/A2) and cognitive variables (black bars). Only full scale IQ, fluid IQ and working memory showed significant correlations with spectral power.



**Relationship between cognitive variables and topographical distribution of sleep EEG power (local analysis)**

In an explorative analysis, correlations between spectral power in the specific bands in NREM sleep and cognitive scores were calculated separately for every individual electrode and illustrated as maps (Figure 4-2). Power maps showed a symmetrical pattern with respect to the anterior-posterior axis with maximum power located over frontocentral areas. A specific (predominantly symmetric) pattern was found for the correlation maps with exclusively positive correlations (maximum r-values ~.70). The maximum of correlation coefficients between full scale IQ and spectral power (10-13.25 Hz; 15.5-20 Hz) was located over central and parietal areas, whereas the pattern for the correlation coefficients between fluid IQ and spectral power (13-20Hz) showed a parietal and a frontal maximum. For both, full scale IQ and fluid IQ, the pattern of correlations did not coincide with areas of highest spectral (which showed maximal power over central regions for the selected frequency ranges), but rather appeared like mirror images with highest correlations over regions with lowest spectral power. The pattern of correlation coefficients between working memory and spectral power (16-20Hz) was rather scattered, with only a few derivations showing correlations between spectral power and scores of working memory.

Figure 4-2: Topographical plots of spectral power and Spearman rank correlations between spectral power and cognitive variables.
Maps on the left represent spectral power in the corresponding frequency ranges (see Fig. 4-1). Maps on the right represent significant correlations between the particular cognitive variables and spectral power in the corresponding frequency ranges. White areas: non significant correlations.




**DISCUSSION**

This study describes the relationship between the children's sleep EEG and their intellectual ability – a relationship which is not only present at a global level, but also involves local components. Correlation coefficients of spectral power in specific frequency ranges and cognitive variables indicated a specific topographical pattern. In contrast to earlier studies reporting neuronal correlates

of intelligence during wakefulness (Duncan et al., 2000; Gray, Chabris, & Braver, 2003; Thatcher, North, & Biver, 2005), the strongest relationships during sleep were not located over frontal areas, but rather over central and parietal areas. In fact, it is well known that the EEG power and power within specific frequency bands of the sleep EEG (Tarokh & Carskadon, 2010) as well as the topographical distribution of the sleep EEG (Kurth, Ringli et al., 2010) changes with age, thus it may be that the topographical focus of correlations between spectral power and IQ scores is indeed located over frontal areas, but only in mature (adult) human brain.

Whereas the earlier reported global relationship between spectral power and intellectual ability could further be specified by local topographical patterns for full scale and fluid IQ, working memory failed to reveal a specific pattern, which may be due to the following reasons: First, the magnitude of correlations in the global analysis was lower for working memory than full scale or fluid IQ (see Figure 4-1). Second, the global analysis was based on C3/A2 derivation, whereas the topographical maps are based on average reference.

Although there are few studies on neurobiological correlates of intelligence during sleep that also involve sleep EEG recording from multiple derivations (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Shaw et al., 2006), to our knowledge, a comprehensive topographical analysis of the relationship between the sleep EEG and IQ scores has not been performed before. Moreover, in the above cited studies, the reason for recording from multiple derivations was not a topographical interest, but the intention to ideally catch/map/identify a particular EEG feature (e.g., the sleep spindles). Besides, there is no single study in children that reports correlations between IQ scores and sleep EEG power derived from multiple electrodes sites.

## CONCLUSION

The present results show that the sleep EEG represents a correlate of children's intellectual ability, as measured by full scale and fluid IQ, which shows local topographical pattern.


## ACKNOWLEGDEMENTS

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# III Discussion

## 3.1 Purpose and methods

The current PhD thesis aimed to identify behavioral and physiological variables of sleep that are related to intellectual ability in healthy, school-age children. No intervention or experimental sleep manipulation has been applied, because the focus was exclusively on trait-like aspects. Both, children's sleep and intellectual ability were comprehensively characterized, using different measurement tools and assessing multiple facets of the two phenomena.

Sleep has been described by the use of questionnaires, actigraphy and PSG, offering quantitative and qualitative data. Variables such as sleep duration, daytime sleepiness, different scores for chronotype, variability of sleep pattern (weekdays versus free days), sleep stages, spectral composition of the sleep EEG and EEG power in specific frequency bands, sleep spindles and topographical aspects of the sleep EEG have been recorded and analyzed.

Intellectual ability has been assessed by the WISC-IV (German version), a multidimensional intelligence test, yielding scores for full scale IQ and separate indices for verbal and fluid IQ, working memory and speed of processing. Besides, data on attentional variables, such as alertness and go/nogo has been collected.

To control for potential confounders, children were also characterized in terms of their pubertal development, handedness, and socioeconomic status and they were screened for psychological problems.

## 3.2 Sleep duration as a behavioral correlate of intellectual ability

On the behavioral level, it could be demonstrated that sleep duration is indeed related to intellectual ability, but contrary to common sense in a negative way (see study I). In contrast to intuitive assumptions, short sleep duration was associated with higher scores of intellectual ability – full scale IQ, fluid IQ and working memory - confirming previous reports of the early 1930s (Erwin, 1934; Reynolds & Mallay, 1933; White, 1931). Interestingly, Gruber and colleagues (2010) recently investigated a small population of children (N=39) aged seven to eleven years and reported an association between short sleep duration and poor

IQ measures. Given that the authors failed to specify how exactly parental report of children's sleep duration was obtained (by personal inquiry or by questionnaire? on scheduled days or on free days? during which period of time?), the results of Gruber and colleagues have, however, to be interpreted with caution. It may be speculated that implicit parental assumptions may have biased the specifications about their children's sleep duration, in the sense that those parents with rather problematic children who do not meet the academic requirements, tend to explain the underachievement of their children with bad quality and quantity of sleep. Thus, we are confident that our approach using a structured questionnaire and actigraphy to assess sleep duration separately for scheduled and free days may be more appropriate. Besides, our results were consistently pointing towards a negative relationship between sleep duration and IQ scores – be it for variables derived from actigraphy or those derived from questionnaires. Moreover, our results are also in agreement with earlier findings from the Zurich Longitudinal Studies which include 493 children and adolescents aged 7 to 14 years (Jenni, Caflisch, & Molinari, 2009).

Children with short sleep duration may benefit from a long wake-time. Being awake offers constant opportunities of cognitive stimulation, social interactions and multisensory input. Thus, one may assume that children characterized by short sleep durations were more stimulated over the years compared to those with longer sleep durations and the accumulated effect may finally be reflected in higher scores of intellectual ability.

Alternatively, the negative correlation between sleep duration and intelligence scores may be explained in light of the *neural efficiency theory* (Haier et al., 1988), stating that "intelligence is not a function of how hard, but rather of how efficient the brain works. This efficiency may derive from the disuse of many brain areas irrelevant for good task performance as well as the more focused use of specific task relevant areas" (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992 ,p. 415-416). The current results would argue for extension of the original theory – referring not only to daytime, but also to nighttime behavior. Children with higher cognitive efficiency, reflected by higher IQ scores, may also display higher nighttime efficiency (i.e., more efficient neuronal recovery), reflected by shorter sleep duration.

### 3.3 Neuronal efficiency from an anatomical perspective

A different perspective that highlights the anatomical basis of neural efficiency, independent from the actual behavioral state (i.e., wakefulness, NREM and REM sleep) is offered by computational biology. The approach followed among others by Li and colleagues (2009), focuses on the biological or anatomical basis of intelligence, assuming that higher intelligence corresponds to more efficient information transfer, which is related to higher global efficiency of brain anatomical networks. According to the network approach (see Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Sporns & Zwi, 2004; Watts & Strogatz, 1998), the "human brain can be viewed as a large interacting and complex network (…), with small-world attributes, characterized by a high clustering index and a short average distance between any two nodes" (Li et al., 2009, p.1). Correlating IQ scores of healthy adults with network properties derived from MRI scans (90 cortical and sub-cortical regions defined with the automatic anatomical labeling and tractography based on diffusion tensor imaging between the previously defined regions), it could be demonstrated that shorter path length between any two nodes and higher global efficiency of the network is related to full scale, fluid and verbal IQ. Global efficiency of the network is defined as the inverse of the sum of minimal path length between each pair of nodes (see Li et al., 2009).

Although the network perspective intuitively makes sense as a theoretical framework for neural efficiency, the results have to be interpreted with caution. Correlation coefficients (controlled for age and gender) are rather low (approximately .25), and they were not corrected for multiple correlations. Thus, the results of Li and colleagues (2009) have to be considered as preliminary and further studies are needed to corroborate these intriguing findings.

### 3.4 Extreme sleep duration as a potential risk factor for mental and physical health

Several studies have shown that lack of sleep is associated with cognitive impairment and behavioral problems in children and adolescents (Dahl, 1996; Nixon et al., 2008; Sadeh, Gruber, & Raviv, 2003; Touchette et al., 2007). These findings have led to the assumption that sleep is critically important, in particular for the developing brain and, thus, short sleep should be avoided. However,

findings of the current PhD thesis indicate that the issue is far more complex. Apart from the relationship between sleep duration, mental health and cognitive functioning, sleep has also been related to general health. In this context, it has repeatedly been reported that the beneficial effects of sleep cannot necessarily be considered linear in nature, i.e. the more, the better. In contrast, the association between all-cause mortality and sleep duration seems to be rather U-shaped (Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Patel et al., 2004; Wingard & Berkman, 1983), indicating that both, too short but also too long sleep durations may be detrimental for several aspects of health, such as for instance cardiovascular diseases. Interestingly, already Hippocrates, an influential physician and philosopher of the Greek epoch stated "Schlaf, wie Schlaflosigkeit, sind beide von Übel, wenn sie das Mass überschreiten" (Sack, 1927 , translated: „Sleep and watchfulness, both of them, when immoderate, constitute disease"). Analyzing more detailed the U-shaped association between sleep duration and mortality, Ferrie et al. (2007) reported that not only the actual sleep duration per se is associated to all-cause mortality, but in particular changes in the habitual sleep duration - increase or decrease. However, effects are only correlational and thus do not allow for conclusions about cause and effect - it may be that an extreme sleep duration causes or reflects pathological processes.

As much as many other health-related variables such as body weight, it may be speculated that sleep duration with its large inter-individual variability (Van Dongen, Vitellaro, & Dinges, 2005) may also be characterized by a large range of tolerance regarding potentially dangerous quantities in general. On top of the general range (large inter-individual variability), sleep duration may have its *individual* optimum for a given person which is beneficial for physical but also psychological health and intellectual performance. In analogy to body weight, one may even argue for a kind of set-point for sleep duration, leaving open what actually represents the individual optimum for a given person and how to assess it.

In fact, recent studies on habitual sleep duration reported that inter-individual differences in sleep duration may primarily reflect self-selected sleep restriction (Klerman & Dijk, 2005), with subjects' approaching an asymptotic sleep duration when given increased sleep opportunity on several consecutive nights (asymptotic sleep duration of 8.2 hours (Wehr et al., 1993) and 8.7 hours

(Rajaratnam, Middleton, Stone, Arendt, & Dijk, 2004)). Consequently, one may assume, that optimal sleep duration is represented by ad lib individually chosen sleep duration, which is free from external, but also self-imposed (e.g., lifestyle factors, self-perceived daytime functioning, etc.) restrictions. The key to physical and psychological health, well- being and cognitive functioning may probably be a sleep duration, timing and behavior that generally match the individual needs.
Eventually, there is a need for further research investigating the relationship between sleep and cognition. In particular, studies should address children's sleep behavior, in order to separate intuitive assumptions from scientific results, and clearly differentiate between descriptive and normative aspects. In this sense, a quote from the early twentieth century by Lewis Terman is nowadays still up to date: "But exactly how much sleep *is* required by this developing organism for its healthy functioning and growth? We have a large number of *estimates based upon opinion and loose observation*, but no answer based on data of scientific validity" (Terman & Hocking, 1913 ,p.138).

### 3.5 The sleep EEG as a physiological correlate of intellectual ability

Sleep duration correlated with different IQ measures in children, and thus can be considered as a *behavioral* nighttime correlate for intellectual ability. Yet, on the *physiological* level, several variables of the sleep EEG are also related to intellectual ability (see study III): First, it has been shown that percentage of NREM sleep is significantly correlated with working memory and speed of processing - the more NREM sleep, the higher the scores of working memory and speed of processing. Second, spectral power in specific frequency bands (clustered in the alpha, sigma and beta range) is related to cognitive variables – full scale IQ, fluid IQ and working memory. The more spectral power in the alpha, sigma and beta range, the higher the scores of intellectual ability. Third, sigma power, individually defined as the area under the sleep spindle peak (relative to the background EEG) significantly correlates with cognitive variables – full scale IQ and fluid IQ. The more power within this individually defined sigma band, the higher the scores of full scale IQ and fluid IQ. The peak frequency itself was, however, negatively related to full scale IQ – the lower the peak frequency, the higher the intellectual ability. Finally, the associations between spectral

power in specific frequency ranges and cognitive variables are not only present on the global level, but also showed local aspects (see study IV).

Given the fact, that many empirical observations have related differences in IQ scores to variations of brain structure and function during wakefulness (Gasser, Von Lucadou-Muller, Verleger, & Bacher, 1983; Jung & Haier, 2007; Thatcher, North, & Biver, 2005), surprisingly little research has been performed to investigate these relations during sleep. The neuronal network properties underlying intellectual differences are supposedly hardwired and thus should be identical regardless of the actual behavioral state (i.e., wakefulness or sleep). In this context, studying the brain during sleep may even be more adequate: Whereas studies performed during wakefulness may be biased by external influences such as attention, motivation or temporal fluctuations in current mood, studies performed during sleep may be less affected by these potential sources of interference. Moreover, studies on functional neurobiological correlates of intelligence during wakefulness are characterized by another inherent problem: It is not possible to ultimately control the baseline condition. This means that for the control condition (no intervention) nobody knows what actually happens when subjects are asked to quietly relax. Some may accidentally fall asleep whereas others are thinking about their day. In fact, the resting state contains persistent brain activity, when subjects are left to think to themselves undisturbed (Mazoyer et al., 2001; Raichle et al., 2001). The brain system involved in internal modes of cognition has become known as the brain's default network (for review see Buckner, Andrews-Hanna, & Schacter, 2008). It may be speculated that this default network with the multitude of differentially involved anatomical structures also involves inter-individual differences. Thus, it may not only be difficult to obtain a well standardized and adequate control condition for the resting state, but also a challenge to minimize these individual differences.

### 3.6 Neuronal correlates of intellectual ability during wakefulness

During wakefulness, it has repeatedly been shown, that specific EEG parameters reflect intellectual ability. Although correlations between variables of the EEG and IQ scores are higher in mentally retarded and those, with a causal link between brain dysfunction and intellectual subnormality (Gasser, Von Lucadou-Muller,

Verleger, & Bacher, 1983), the relationship persists also for healthy subjects. In particular, spectral alpha power is positively correlated with intellectual ability – the higher the alpha power in vigilance state awake (eyes closed), the higher the IQ scores (Jausovec, 1996; Klimesch, 1999; Schmid, Tirsch, & Scherb, 2002; Thatcher, North, & Biver, 2005). It is important to note that in a minority of healthy adults, the posterior alpha rhythm may not be detectable (Niedermeyer, 1997).

From animal models, clinical studies and neuroimaging data, it is known that the generation and modulation of alpha rhythms strongly depends on thalamic activity, which is not exclusively evoked by isolated thalamic "pacemakers", but rather result from complex interactions between cortical and thalamic oscillators, involving thalamocortical loops (Buzsaki, 1991; Hughes & Crunelli, 2005; Schreckenberger et al., 2004; Steriade, 2000).

Based on these neuroanatomical findings, it may be hypothesized that the maturation of the neocortex and the thalamocortical loops determine the efficiency of the system, responsible for the generation of the alpha rhythm. Children advanced in terms of cortical maturation (e.g., number, spreading or pruning of synapses) and the development of thalamocortical circuits may display a more well-defined alpha rhythm. On the psychological level, those advanced in brain maturation probably score higher in tests of intellectual ability. Thus, maturation of the neocortex and efficiency of the thalamocortical loops, which is reflected in alpha activity, may represent one of the underlying biological bases of intellectual ability.

Even though there is also alpha activity during sleep, it has, up to now, not been investigated whether there is also a relationship between scores of intellectual ability and alpha activity during sleep. In fact, in our population of healthy school-age children, there was a significant positive correlation between alpha power in NREM sleep (C3A2) and full scale IQ scores (see study III). Yet, it has to be considered that the topographical pattern of EEG power in general and thus also of alpha activity is different for the different behavioral states (wakefulness, NREM and REM sleep). During NREM sleep, alpha activity is characterized by a frontal maximum, contrasted with an occipital maximum of alpha activity during REM sleep and wakefulness (Tinguely, Finelli, Landolt, Borbély, & Achermann, 2006). Eventually, it may be speculated that characteristics of the human EEG - independent of the actual behavioral state (sleep or wakefulness) - and

intellectual ability are epiphenomena of the same underlying structure, representing different facets of the same individual trait.

### 3.7 Neuronal correlates of intellectual ability during sleep

During sleep, the few existing studies in adults have all pointed towards an important role of sleep spindle activity or sigma power for intellectual ability (Bódizs et al., 2005; Fogel, Nader, Cote, & Smith, 2007; Schabus et al., 2006; Schabus et al., 2008). The study performed during the present thesis reported for the first time a similar relationship in healthy school-age children. Individually defined sigma power correlated positively with children's intellectual ability (full scale and fluid IQ).

Sleep spindles are oscillations that are generated in the thalamus, but also involve the cerebral cortex and synchronization from reciprocal thalamocortical projections (Steriade, 2003; Steriade, McCormick, & Sejnowski, 1993). As such, it may be speculated that sleep spindles just as alpha rhythms depend on maturation of the neocortex and efficiency of the thalamocortical loops. Along the same lines, it has been suggested that the relationship between sigma power and fluid IQ may reflect efficiency of information processing, dependent on thalamocortical communication (Fogel, Nader, Cote, & Smith, 2007).

Whether the association between alpha activity and intellectual ability during wakefulness is functionally related to the association between sleep spindle activity and intellectual ability during sleep remains yet to be determined - both associations may reflect maturation of the neocortex and efficiency of the thalamocortical circuits.

### 3.8 Relationship between sleep spindles and intellectual ability

It is an ongoing debate, whether sleep spindles represent a unitary entity or rather two distinct phenomena with different functional roles – slow spindles, with a frequency of below 12 Hz and a predominant frontal localization (derived from surface EEG recordings), and fast spindles, with a frequency of about 14 Hz and a rather centroparietal localization (Schabus et al., 2007; Zeitlhofer et al., 1997). It has been suggested that slow spindles may in fact represent anterior peaks of alpha activity during NREM sleep (De Gennaro & Ferrara, 2003). Based

on the reported association between alpha activity and intellectual ability, anatomical structures involved in the generation and synchronization of alpha and sigma rhythm, one may expect associations between slow spindle activity and intellectual ability. On the other hand, based on data about the cortical activation pattern, it has been proposed that in particular fast spindles are involved in the processing of sensorimotor and mnemonic information (Schabus et al., 2007). Following this line of evidence, one may rather focus on the fast spindles as a candidate mechanism, potentially related to differences in intellectual ability.

In our population of prepubertal children aged 10.5 (±1.0) years old, four out of fourteen children visually displayed two spindle peaks in the power spectrum (C3A2). Given the small number of subjects in general and the small number of subjects displaying two spindle peaks, it was not possible to perform separate analysis, comparing slow versus fast sleep spindles. However, it may be that the two types of sleep spindles would have been detectable by analysing the power spectrum of frontal electrode sides instead of the C3A2 derivations. In any case, there was a single dominant peak in the power spectrum (C3A2) of all of our subjects. The mean frequency of the dominant peak in the power spectrum was located at 12.5 (±0.4) Hz which rather corresponds to slow spindles, whereas the topographic distribution of the spindle peak was located over centroparietal areas (see study IV), which rather relates to fast spindles (De Gennaro & Ferrara, 2003; Schabus et al., 2007; Zeitlhofer et al., 1997). It has previously been reported that the peak spindle frequency (Jenni & Carskadon, 2004; Tarokh & Carskadon, 2010) and the topographical distribution of sigma power (Kurth, Ringli et al., 2010) dramatically changes with age. Furthermore, it has been suggested that the two types of sleep spindles show different time courses of maturation, with centroparietally located fast spindles increasing linear with age, and frontally located slow spindles abruptly emerging during puberty (Shinomiya, Nagata, Takahashi, & Masumura, 1999). Our study population of prepubertal children was too small and with a limited age range for the detection of potentially distinct spindle types. Consequently, we could neither contribute to the discussion of one versus two types of sleep spindles, nor could we assign a functional role for cognitive processing/intellectual ability to either type of sleep spindles.

### 3.9 Bridging the gap - neuronal correlates of learning and intelligence during wakefulness

Apart from the general paucity of work on neuronal correlates of intellectual ability during sleep, there are up to now only a few studies, investigating learning (state-dependent), general intellectual ability (a trait) and its physiological correlates of the brain in a combined approach.

During wakefulness, state-dependent cognitive variables and the general trait (learning and intelligence) seem to be closely interlinked and associated with neurobiological correlates. For example, in a study assessing event-related desynchronization (ERD) during a reasoning task in a pre-test – training – post-test design, Neubauer et al. (2004) linked state-dependent learning and trait intelligence to cortical activation in the following way: "the higher the subjects' general mental ability, the larger the decrease in the amount of cortical activation" following a training session (Neubauer, Grabner, Freudenthaler, Beckmann, & Guthke, 2004 ,p.66). The authors concluded that more intelligent subjects may benefit more from training with respect to their neural efficiency, thus bridging the gap between learning and intelligence. These results were also supported from another study using the glucose metabolism rate (GMR) as a correlate of neural efficiency. Applying a visuo-motor learning task (Tetris computer game) and comparing the GMR during the first learning session with the GMR during following practice sessions, subject's decrease in whole-brain GMR across sessions correlated with their general psychometric intelligence; those with the highest IQ scores were characterized by the largest decrease in GMR (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992). The authors interpreted this decrease of metabolism from test to retest as support for the neural efficiency effect, claiming that higher intelligence is related to higher neural efficiency and thus less effort necessary for a given cognitive performance.

### 3.10 Bridging the gap - neuronal correlates of learning and intelligence during sleep

During sleep, there is up to now only a single study, investigating learning, intelligence and related neuronal correlates in a combined approach. Schabus and colleagues (2008) assessed subject's general intelligence and compared sleep spindle activity in the night following a paired-associate word learning task

or a non-learning control task. Spindle activity was generally elevated in highly gifted subjects, but increase of spindle activity (control night versus learning night) was specifically related to learning improvement, independent of subject's general intellectual ability, which contradicts results form studies during wakefulness (e.g., Haier, Siegel, Tang, Abel, & Buchsbaum, 1992; Neubauer, Grabner, Freudenthaler, Beckmann, & Guthke, 2004). Schabus and colleagues (2008) concluded that "spindle increase after learning is related to elaborate encoding before sleep, whereas an individual's general learning ability is well reflected in inter-individual (and trait-like) differences of absolute sleep spindle activity" (Schabus et al., 2008 ,p.127).

Given the close conceptual and empirical relation between general intelligence and learning, it seems however hardly plausible to understand these as completely unrelated and separate entities, without any common ground or physiological basis. The close conceptual link between learning and intelligence was among others prominently expressed by Thorndike: "Estimates of intelligence should be estimates of the ability to learn" (Thorndike, 1924 ,p.17). It has to be emphasized that the evidence for an independence of learning and intelligence reported by Schabus and colleagues (2008) is only based on a single learning task (paired-associate word learning). Probably, the instruction to visually imagine the two words presented in a given trial may indeed foster learning, but also influence the spindle activity quantified during the following night in an even more complex manner. Thus, the increase in spindle activity following the learning session may not only be driven by the intended learning effect, but exclusively or additionally by the elaborate visual encoding.

Consequently, the relationship between variables of sleep on the one side and learning (as a state-dependent specific cognitive process) and intelligence (a trait) on the other side remains unsettled and equivocal, and calls for further clarification.

### 3.11 Process-oriented intelligence testing as an alternative approach to link trait intelligence and state-dependent learning

A different and promising view about the nature of intelligence is offered by plasticity- or process- instead of status-oriented performance assessments. Whereas the classical status-oriented psychometric test theory claims exact

replication of results as an indicator of high reliability, the process-oriented testing approaches are in fact based on the variance which results from repeated testing. Instead of striving to eradicate this otherwise considered error variance, process-oriented testing assumes that the variance is not necessarily ascribable to deficits of the testing procedure, but reflects the innate learning capacity of an individual, indirectly pointing toward the individuals' intellectual ability (Guthke & Wiedl, 1996 ,p.4).

Key elements of process-oriented intelligence testing often consists of: (1) Adaptive testing, (i.e., progression from easy to more difficult test items), whereby adaptability is not based on group statistics but on individual performance of the subject, (2) Continuous feedback of individual performance and (3) Information and help in realization of concrete strategies (elaborated feedback) (Carlson & Wiedl, 1980). In brief, the simplest way of process-oriented testing can be described as a pretest – training – posttest design (Kühl & Baltes, 1988).

Although the different process-oriented approaches concurrently formulated by several research groups (for instance, the "*learning test concept*" (e.g., Guthke, 1982), the *"learning potential assessment*" (e.g., Budoff, 1987), and the "dynamic assessment" (e.g., Brown & Campione, 1986)) all focus on different aspects, there are nevertheless certain similarities: Process-orientation originates from prognostic questions in the clinical context, and has mainly been used for developmental assessments in children (Brown & Ferrara, 1985) and for gerontopsychological assessments (Kühl & Baltes, 1988). The purpose of these approaches is to evaluate and determine the *potential* capability rather than the *actual* status of an individual. For example, the learning potential assessment has been developed to differentiate between mentally retarded and "educationally retarded" children (e.g., Budoff, 1987). Process-oriented approaches have also successfully been applied for the early diagnosis of dementia (Kühl & Baltes, 1988). Regardless of the target group or actual question, an important distinction in the context of process-oriented testing refers to "*baseline performance*", "*baseline reserve capacity*" and "*developmental reserve capacity*". "*Baseline performance*" reflects the actual performance level (status) and corresponds to test scores of classical psychometric testing. "*Baseline reserve capacity*" and "*developmental reserve capacity*" are, however, unique concepts of process-oriented approaches, representing an achievement

potential which may or may not be realized. "*Baseline reserve capacity*" is considered the realization of a presently existing capacity under optimal conditions ("current maximum performance"), whereas "*developmental reserve capacity*" is assumed to represent the "future maximum performance" that may become realizable by the teaching of strategies and the development of new cognitive schemata (for review see Kühl & Baltes, 1988).

Up to now, studies either focused on narrowly defined aspects of specific learning tasks (e.g., perceptual learning, paired-associate word learning) or global intellectual ability in relation to neuronal correlates. However, the application of both – the status-oriented and the process-oriented approach - in a combined framework may be promising in bridging the gap between state-dependent learning and trait intelligence. Using process-oriented in addition to the classical status-oriented approaches, the phenomenon of neural efficiency may probably be specified - be it during wake or be it during sleep.

### 3.12 Critical evaluation of this PhD thesis

When interpreting the studies of the present thesis, some limitations have to be considered: First, only a single age-group (school-aged prepubertal children) was investigated and thus, it is not possible to draw any conclusions regarding developmental aspects of the effects reported in the individual studies. Ideally, the study population should have included also a group of adolescents or younger children. Second, due to practical reasons and ethical concerns, it was not possible to collect blood samples and screen for specific genetic polymorphism that are known to influence certain aspects of sleep regulation and daytime cognitive performance. Third, the sample size has been relatively small, thus limiting the statistical power. The population was affected by a sampling bias which inherently characterizes these experimental studies based on voluntary participation, but nevertheless reduces the generalizability of the results. Finally, the experimental conditions, especially those during the sleep EEG recordings were not under optimal control, due to the following reasons: The recording sessions were held in a hospital environment, which implies that timing and procedure of the recording is considered subordinate to the clinical routine. Moreover, the sleep EEG recordings were performed in collaboration with another research group, which required to compromise about the concrete procedure and

the conditions of the recordings. In sum, these concomitants of the EEG recording sessions resulted in a reduced standardization, potentially masking effects. However, sleep EEG recordings in children may in general represent a particular challenge because of parental concerns and demands which have to be considered as well as children's individual needs which have to be met. Because of these inherent characteristics of research in children, another standard in terms of the general demands for standardization has to be applied - a standard that makes adequately allowance for the special conditions.

### 3.13 Implications for further research

The following steps should be taken to further illuminate the relations between sleep, cognitive processing, intelligence and learning: First, insights from different vertical levels (from molecular research to systems level approaches) have to be integrated. Second, different horizontal levels (disciplines involved in the field such as psychology, biology and computing science) need to collaborate. Third, paradigms of different schools of thoughts should be combined and included in a common eclectic model. For instance, it would be promising to apply a process-oriented learning test in addition (not as a competing alternative) to a classical status-oriented test. Up to now, learning has mainly been considered as singular cognitive process but not generally, as an ability to learn. In other words investigating state-dependent learning processes and the general intellectual ability as a trait in a conjoint framework may eventually help to elucidate the physiological basis of these psychological phenomena. Fourth, the relations between sleep, cognitive processing, intelligence and learning should also be investigated in specific age-groups, such as children and healthy elderly, which have largely been ignored so far. Given that sleep as well as cognitive processes and intellectual ability are subjected to substantial age-related changes, there is a need to include different age groups.

In summary, an integrated view of brain functioning regardless of the actual behavioral state – during wake or during sleep – but at the same time accounting for the dynamics of brain maturation may be a promising starting-point to create a basic idea of what could be part of the biological fundament of human intelligence.

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# Appendix

The Pediatric Daytime Questionnaire (PDSS) (modyfied Drake et al., 2003)

Versuchspersonennummer: Datum:
Versuchsdurchführung:

Name:

Vorname:

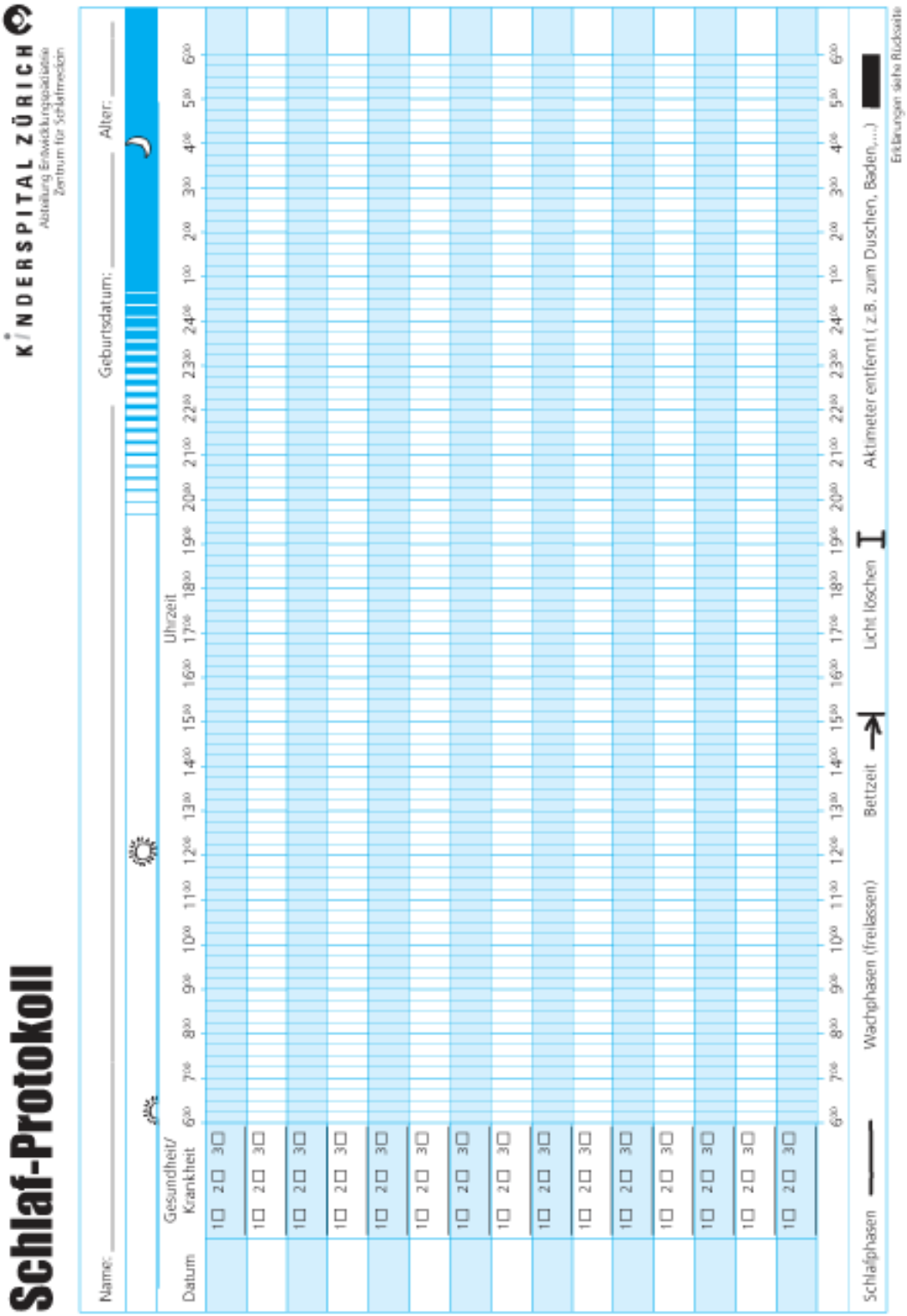
Wer füllt den Fragebogen aus: ☐ Mutter ☐ Vater ☐ Andere

Die folgenden Fragen beziehen sich auf das *normale* Alltagsleben Ihres Kindes in der letzten Zeit. Bitte versuchen Sie sich vorzustellen, wie sich die unten beschriebenen Situationen auf Ihr Kind auswirken würden, auch wenn Sie sie in genau dieser Form möglicherweise noch nicht erlebt haben.

**Für wie wahrscheinlich halten Sie es, dass Ihr Kind in den folgenden Situationen tatsächlich einnickt oder einschläft (sich nicht einfach nur müde fühlt)?**

| **Situation** | **Wahrscheinlichkeit** | | | |
|---|---|---|---|---|
| Wie oft schläft oder nickt Ihr Kind während des Unterrichts ein? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft schläft oder nickt Ihr Kind während der Hausaufgaben ein? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Ist ihr Kind während der grössten Zeit des Tages wach und munter? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft ist Ihr Kind müde und mürrisch während des Tages? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft fällt es Ihrem Kind schwer, morgens aus dem Bett zu kommen? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft schläft Ihr Kind nachdem es morgens geweckt wurde noch einmal ein? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft muss Ihr Kind morgens geweckt werden? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |
| Wie oft haben Sie das Gefühl, Ihr Kind bräuchte mehr Schlaf? | nie □ | selten □ | manchmal □ | oft □ sehr oft □ |

Sleep diary (adapted from the sleep diary used at the Child Development Center, Children's University Hospital Zurich)



# Curriculum Vitae

| | |
|---|---|
| Name: | Anja Geiger |
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| October 2005 | Diploma degree in Psychology, University of Konstanz, Germany |
| | Certificate „German as a foreign language" |
| October 1999 – 2005 | Studies in psychology, University of Konstanz, Germany |
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| | Thesis: "Hemispheric contributions to the processing of emotions in chimeric faces – behavioural and electrophysiological evidence" |
| September 2003 – April 2004 | Research placement in cognitive neuroscience, University of Glasgow, U.K. |
| February 2003 – April 2003 | Clinical placement in neuropsychology, University Hospital of Ulm, Germany |
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